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DR. E. B. KRUMBHAAR

This issue marks the retirement of Dr. Edward Bell Krumbhaar as Editor of the American Journal of the Medical Sciences. First as Associate Editor with Dr. John H. Musser, Jr., 1922 to 1924 both inclusive, then as Editor from 1925 through 1950, Dr. Krumbhaar has completed 29 years of service to the Journal, or longer than any former Editor, save only Dr. Isaac Hays.

The span of Dr. Krumbhaar's Editorship covers an era that saw more, greater and more rapid advances in medicine than occurred in all the preceding 122 years of the Journal's existence. That the Journal maintained its position in the vanguard of medical publications throughout this period has been his accomplishment. He brought to his task a background of training and a breadth of interest and activities that can best be appreciated in the light of some of the positions he has held and of what he has written: Associate in Medicine, Assistant Professor of Research Medicine, and Professor of Pathology in the University of Pennsylvania; Cardiologist to the Hospital of the University of Pennsylvania; Director of Laboratories of the Philadelphia General Hospital; Lt. Colonel, MRC, U. S. Army (Service in France, 1917-19); Member of the Board of Overseers, Harvard University, and Chairman of its Committee to Visit the School of Public Health; author of "Spleen and Anemia," "History of Pathology," and of over 200 medical articles and chapters in textbooks, including the forthcoming new edition of Musser's "Internal Medicine." Editor and Translator of the two English editions of Castiglioni's "History of Medicine;" Editor of Clio Medica. With such a many-sided equipment he has combined a deep interest in medical journalism and the keen feeling of responsibility that lies upon a medical editor.

The limits of space prevent a citation of the major contributions that have appeared in the Journal during Dr. Krumbhaar's Editorship. The list of authors would include the leaders in medicine of this country and Canada. Moreover, there would be found articles from other lands in greater numbers than ever before. A comparison of issues in 1924 and in 1950 would show notable improvements both in form and substance.

Now retired from his academic duties, Dr. Krumbhaar plans to devote himself to his avocation of a lifetime: medical history. The incoming Editor takes this opportunity to express gratitude for his training in medical journalism to his former Chief, under whom he served a 26-year apprenticeship, and to wish him many more happy and productive years.

THE AMERICAN JOURNAL OF THE MEDICAL SCIENCES

JANUARY, 1951

PNEUMOCOCCAL PNEUMONIA AT JEFFERSON HOSPITAL

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AND
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In recent years the importance of pneumonia has decreased considerably, especially as a cause of death. Suggestions have been made, although not proven, that there has been a decrease in the rate of admission of patients with pneumonia to hospitals. Others have pointed out the changing nature of the disease[3,4] per se, regardless of the effects of antibiotic therapy on the mortality and morbidity. The question as to whether antibiotic therapy has had any effect on the types producing disease existed in our minds. Investigators have shown that in recent years the disease is appearing with greater frequency in higher age groups[3,7]. With these points in mind we decided to compare the disease as it is seen now with that seen 10 years ago.

Material. The material studied consisted of the case records of patients admitted to the medical wards with the diagnosis of pneumococcal pneumonia. Two groups of patients were studied. Group I consisted of patients admitted between January, 1937, and January, 1940. There were 75 cases in this group. Group II consisted of patients admitted between October, 1946, and October, 1949. There were 91 patients in this group. In all these cases routine laboratory studies were performed comprising complete blood counts, pneumococcal typing, blood culture, and roentgenogram of the chest prior to starting treatment.

Results. Rate of Admission. The rate of admission of pneumococcal pneumonia for each 3-year period is illustrated in Table 1. The number of cases per 1000 ward admissions were 10.6 for the period, 1937 to 1940, and 10.5 for the period 1946 to 1949. The similarity in rate of admission is of interest when one takes into consideration that with the advent of antibiotic therapy many cases of pneumococcal pneumonia are treated at home successfully. In contrast with our findings, Watson[7], reporting from New Zealand, and Thompson[5] from Cincinnati showed a fall in incidence of pneumonia admissions during recent years.

Bacteriologic Examination. Typing of the pneumococci, either directly or by mouse peritoneal inoculation, and cultures were obtained in all cases. Blood culture was obtained upon admission prior to therapy. Subsequent

blood cultures were taken only in those patients with bacteremia.

Although our groups are relatively small, changes were seen in the types of pneumococci isolated (Table 2). It appears that during recent years there has been an increase in the occurrence of higher numbered types (Type 4 and higher) with a corresponding fall in lower numbered types, especially Type 1. Others also note a trend in this direction. Table 3 illustrates the breakdown of the types of pneumococci isolated by various workers into Type 1, 2, 3, and Group IV. Representative groups studied in the United States have been chosen covering the period 1917 to 1949. There appears to be a gradual decline in the occurrence of Type 1 pneumonia with a corresponding increase in Group IV, that is, the higher numbered types. This is also borne out by comparing our 2 groups. From 1937 to 1940 the incidence of Type 1 pneumonia was 25.3% and from 1946 to 1949 the incidence was 12.0%. Group IV on the other hand has increased from 49.3% in 1937-1940 to 61.5% in 1946-1949. Table 2 indicates that this rise is due to the appearance of relatively less common types, such as Types 12, 17, 23 and 33.

Bacteremia was observed in 8 cases (10.6%) in our Group I and 4 cases (4.4%) in Group II.

TABLE 1.—FREQUENCY OF PNEUMONIA ADMISSIONS

Year	*Pneumonia Admissions*	*Medical Admissions*	*Pneumonia Admissions per 1000*
January, 1937 to January, 1940	75	7041	10.6
October, 1946 to October, 1949	91	8644	10.5

TABLE 2.—FREQUENCY OF TYPES OF PNEUMOCOCCUS

	January, 1937 to January, 1940		*October, 1946 to October, 1949*	
Type	*No. of cases*	*%*	*No. of cases*	*%*
I	19	25.3	11	12.1
II	7	9.3	11	12.1
III	12	16.0	13	14.3
IV	8	10.7	7	7.7
V	4	5.3		
VI	1	1.3	4	4.4
VII	7	9.3	7	7.7
VIII	10	13.3	6	6.6
IX			3	3.3
X	1	1.3	1	1.1
XII			7	7.7
XIV	2	2.7	4	4.4
XV	1	1.3	2	2.2
XVI			1	1.1
XVII			3	3.3
XVIII			1	1.1
XXII	2	2.7	2	2.2
XXIII			6	6.6
XXVII	1	1.3		
XXXIII			2	2.2

TABLE 3.—COMPARATIVE FREQUENCY OF TYPES (U. S. A.)

Author	*Year*	*Types (%)*			
		I	*II*	*III*	*Group IV*
1. Schorer *et al.*[6]	1917–18	30.7	14.9	17.8	36.9
2. Thomas[6]	1917–21	25.1	10.9	14.6	49.4
3. Cecil *et al.*[1]	1921–26	33.6	19.1	13.3	33.3
4. Jefferson Hospital	1937–40	25.3	9.3	16.0	49.3
5. Israel *et al.*[3]	1940–41	18.9	4.6	13.1	63.4
6. Dowling *et al.*[2]	1947	12.1	12.7	14.0	61.2
7. Jefferson Hospital	1946–49	12.0	12.0	14.2	61.7

AGE. Analysis of our data reveals that in Group I, 50% of the patients were distributed between the ages of 31 and 50, while in Group II, 35.3% fell in this age group. The percentage of patients below 31 years of age fell from 22.7% in Group I to 16.4% in Group II, and the percentage above 50 years of age increased from 26.6% in Group I to 47.2% in Group II. The mean age has increased from 39.9 years in Group I to 49.6 years in Group II. This is illustrated in Fig. 1. The increase of the incidence of the disease in higher age groups has also been pointed out by others[3,7].

PHYSICAL FINDINGS. We have been struck by the relative infrequency with which typical physical findings of lobar consolidation are being encountered in recent years. Typical findings of lobar consolidation were found in 84% of cases in Group I, as compared with 47.1% of cases in Group II. Is this an indication of the changing nature of the disease?

COMPLICATIONS. The percentage of purulent complications fell from 16% in Group I to 7.7% in Group II. There were 8 cases of empyema, 3 cases of pneumococcic otitis media, and 1 case of toxic myocarditis in Group I as compared with 5 cases of pleural effusion, 1 case of empyema and 1 case of acute pericarditis in Group II. The development of septic complications is known to increase the mortality rate. Of the 12 cases in Group I who developed such complications, 6 (50%) died. Of the 6 cases in Group II, 3 (50%) died. The decrease in the percentage of septic complications in Group II is probably the result of antibiotic therapy.

MORTALITY. In comparing both groups, the drop in mortality rate is

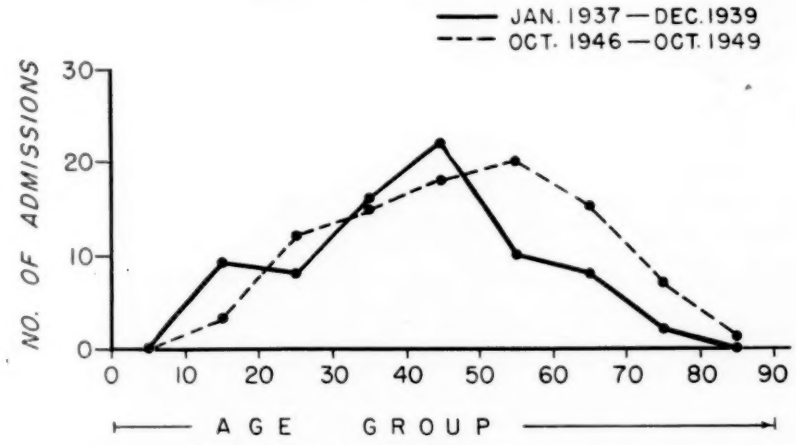

FIG. 1.—Admissions in relation to age group.

striking. There were 16 deaths in Group I with a mortality rate of 21.3%; there were 6 deaths in Group II with a mortality rate of 6.5%. If the mortality rate per year is determined for Group I, 27% died in 1937 and 1938. In those years treatment consisted of type-specific serum, Roentgen-ray irradiation or symptomatic therapy. In 1939 there was a fall in mortality rate to 5%. This decrease corresponds to the institution of sulfonamide therapy in 13 of the 20 cases seen. All patients in Group II were treated with penicillin. The mortality rate in the penicillin-treated group is in accordance with the report of others[2,3,5].

The relation of advancing age to fatality rate is evident in Table 4. Above the age of 40, 28.5% of patients in Group I died, whereas 9.9% of such patients in Group II died. The majority of these patients presented the complicating features of chronic degenerative diseases. Below the age of 40, 15.1% of patients in Group I died while none in this age group died in Group II. The presence of complicating diseases after the age of 40 despite advent of antibiotic therapy is still of important prognostic significance.

Summary. A comparative study has been made of pneumococcal pneumonia as seen at Jefferson Hospital in the years 1937 to 1940 and 1946 to 1949. There has been no decrease in the rate of admission of patients with pneumococcal pneumonia. In recent years (1946 to 1949) there has been an increase in the occurrence of higher types with a corresponding fall in lower types, especially Type I. There has been an increase in incidence of the disease in higher age groups, with an increase in mean age from 39.9 years to 49.6 years. Typical physical findings of lobar consolidation were found in 84% of cases in Group I as compared with 47.2% of cases in Group II. The percentage of septic complications fell from 16% to 7.7%. This is probably the result of antibiotic therapy. The overall mortality rate fell from 21.3% to 6.59%. Above the age of 40, the presence of chronic degenerative disease influences the mortality rate unfavorably.

TABLE 4.—MORTALITY AND ITS RELATION TO AGE

	January, 1937 to January, 1940			*October, 1946 to October, 1949*		
Age Group	*No. of cases*	*No. of deaths*	*% of deaths*	*No. of cases*	*No. of deaths*	*% of deaths*
10–20	9	0	0	3	0	0
21–30	8	1	1.3	12	0	0
31–40	16	3	4.0	15	0	0
41–50	22	6	8.0	18	1	1.1
51–60	10	2	2.7	20	0	0
61–70	8	4	5.3	15	3	3.3
71–80	2	0	0	7	2	2.19
81–90	0	0	0	1	0	0
	75	16	21.3	91	6	6.59

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TREATMENT OF FRIEDLÄNDER'S PNEUMONIA

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It is becoming increasingly apparent that chemotherapy and antibiotic therapy have wrought much improvement in the results of pneumonia due to the Friedländer bacillus[2,4,6]. However there has been considerable disagreement among authors as to the relative value of the agents available in the treatment of this disease[2-6]. Hyde and Hyde, for example, found sulfonamides to be of definite value for this infection and reported only a 13% mortality when the cases were given early treatment[2]. However, Perlman and Bullowa, using sulfonamides, had an 84% mortality in 37 cases[5]. The report of the National Research Council on the use of streptomycin in infections was optimistic as to the value of streptomycin[4], and most recently, Wylie and Kirschner[6] have stated that streptomycin is the drug of choice[6]. It is the purpose of this communication to give an account of experience obtained at Pennsylvania Hospital in the handling of Friedländer's pneumonia during the era of specific therapy.

Incidence. For the years 1938 through 1949, 25 cases of Friedländer's pneumonia have occurred among 2000 pneumonias of all kinds, an incidence of 1.2%. This agrees in general with previously published figures as summarized by Julianelle[3]. Our cases have been grouped as follows: 1, *Acute Primary Friedländer's Pneumonia*: 15 cases. These patients had an acute pneumonia seen soon after onset, their sputa showed only or predominantly Friedländer bacilli, and they had chest films that were consistent with such an infection. In a few who died before much study could be done, the autopsy findings were those of Friedländer's pneumonia. The incidence, then, of acute primary Friedländer's pneumonia is 0.8%.

2, *Acute Mixed Infections or Secondary Friedländer's Infections*: 7 cases. These had, (a) mixed pathogens in the sputum early in the course of illness when first seen, or (b) developed Friedländer's infection in a previous pneumococcal pneumonia, or (c) came to the hospital with a fairly long-standing untreated pneumonia and sputum showing predominantly Friedländer's bacilli but without the Roentgen-ray changes expected with a well advanced Friedländer infection. The other pathogen found in all 7 cases was the pneumococcus.

3, *Chronic Friedländer's Pneumonia*: 3 cases. All were of several months' duration when first seen and had sputa with mixtures of organisms but predominantly Friedländer bacilli and Roentgen-ray changes consistent with a long-standing Friedländer's infection.

As with all published series of cases, this group was composed predominantly of middle-aged males: 21 males with an average age of 47.

Clinical Findings and Diagnosis in the Acute Groups. All patients were acutely ill on admission and complained of acute onset of chills, fever, cough, chest pain and malaise or, in some cases, collapse. All but 2 cases had some physical signs consistent with a pneumonia. The 2 exceptions

were thought to have myocardial infarction and died in a few hours. The diagnosis was made bacteriologically and ante mortem in 17 cases and post mortem only, in 5 cases. Temperatures ranged from 100 to 105°F.

In no case was diagnosis facilitated by the character of the sputum which was variously described as "bloody", "rusty", "white", or "none" but never in textbook fashion as "stringy" or "sticky". Nor was the initial Roentgenogram of much more value than to confirm the presence of a pneumonia, some lobular, and some lobar. A few Roentgen-ray reports mentioned "consistent with Friedländer's infection" because of tissue breakdown and cavitation in a pneumonic process. White blood cell counts varied without consistency from leukopenia to marked leukocytosis. Though blood culture was positive in 31% of those taken, it was not of importance in making the initial diagnosis. The diagnosis rests primarily on bacteriologic evidence of Friedländer bacilli in the sputum or throat.

Clinical Findings and Diagnosis in the Chronic Group. These patients had long-standing weakness, malaise, and productive cough that produced Friedländer's bacilli in a varied flora. All gave a history of having had pneumonia months previously. Their roentgenograms showed cavitation and fibrosis in varying degrees.

Mortality. The crude mortality for the entire series is 10 of 25 cases (40%). Of the 22 acute cases it is 10 of 22 (46%).

Of the 15 acute primary cases it is 8 of 15 (53%).

The mortality of the 7 acute mixed and secondary cases is 2 of 7 (30%), which is certainly several times higher than for pure pneumococcal pneumonia and yet less than for pure Friedländer's pneumonia. None of the chronic cases died and none of the females died.

In relating mortality with time elapsed before institution of specific treatment, it was found that an average of 4.1 days with symptoms elapsed before onset of therapy in those who subsequently died and 2.9 days with symptoms elapsed before treatment in those who recovered in the acute group of 22 cases.

The relation of blood stream infection to mortality is interesting: 31% of the blood cultures taken grew out Friedländer's bacillus (5 of 16), and 80% of these patients died. With negative blood culture the mortality was 18%. Blood culture finds its main usefulness in prognosis rather than in diagnosis.

Treatment and Results. Of the chronic cases, one ran the gamut of drugs: sulfonamides of various types, penicillin, and streptomycin, and when last seen still harbored Friedländer's bacilli and had marked pulmonary fibrosis. She has refused further treatment with newer antibiotics. One patient cleared his sputum on sulfonamide and streptomycin, and one received no specific treatment and died 1½ years later of non-specific bronchopneumonia and emphysema with no Friedländer's bacilli on culture of sputum. No autopsy was obtained.

The 22 acute cases received various treatments as shown in Table 1.

Of 11 patients given sulfonamides with 3 deaths, most received sulfadiazine, some sulfathiozole and 1 got sulfanilamide. Of the 5 receiving only penicillin, all died. Of the 4 receiving some combination of sulfonamide, streptomycin and penicillin, all recovered. The 2 that received no drug therapy died; omission of these from the calculations gives a mortality of 40% for specific therapy of all types in the acute cases.

Tables 2 and 3, with the acute group

TABLE 1.—RESULTS OF TREATMENT OF ACUTE FRIEDLÄNDER'S PNEUMONIA

Drug	*Cases*	*Deaths*	*Mortality (per cent)*
Sulfonamides only	11	3	27
Streptomycin only	0	–	—
Penicillin only	5	5	100
Penicillin & Sulfonamides	1	0	0
Penicillin & Streptomycin	2	0	0
Sulfonamides & Streptomycin	1	0	0
No specific treatment	2	2	100
Totals	22	10	46

TABLE 2.—RESULTS OF TREATMENT OF ACUTE PRIMARY CASES

Drug	*Cases*	*Deaths*	*Mortality (per cent)*
Sulfonamides only	8	1	12.5
Penicillin only	5	5	100
No specific treatment	2	2	100
Totals	15	8	53

TABLE 3.—RESULTS OF TREATMENT OF ACUTE MIXED AND SECONDARY INFECTIONS

Drug	*Cases*	*Deaths*	*Mortality (per cent)*
Sulfonamides only	3	2	66
Penicillin & Streptomycin	2	0	0
Penicillin & Sulfonamides	1	0	0
Sulfonamides & Streptomycin	1	0	0
Totals	7	2	30

TABLE 4.—YEARLY INCIDENCE OF ACUTE FRIEDLANDER'S PNEUMONIA *VS.* TREATMENT AND MORTALITY

Years	*Cases*	*Treatment*		*Deaths*	*Mortality (per cent)*
1938–1939	2	Sulfonamide	1		
		None	1	2	100
1940–1941	7	Sulfonamide	7	1	14
1942–1943	1	Sulfonamide	1	0	0
1944–1945	2	Sulfonamide	2	1	50
1946–1947	3	None*	1		
		Penicillin	1*	2*	66
		Sulfonamide & Penicillin	1		
1948–1949	7	Penicillin & Streptomycin	2		
		Penicillin only	4*	4*	57
		Sulfonamides & Streptomycin	1		
Totals	22			10	46

NOTE: Asterisks relate treatment and death

divided into its component parts, show that while sulfonamides alone controlled acute primary Friedländer's pneumonia, combinations of drugs seem to have better effect in the mixed and secondary infections.

Table 4 shows in this small series how treatment has changed, with the passage of years, since the introduction of specific drug therapy in 1938 and how mortality has actually increased as the use of sulfonamides decreased and the use of penicillin increased.

Comparing the years 1940-1941 and 1948-1949, each with 7 cases (Table 4), certain interesting features can be seen. The year 1940-1941 was a sulfonamide year exclusively, and the mortality rate was 14%. The year 1948-1949 was one of varied treatment, and the mortality was 57%, with penicillin being the drug involved in these latter deaths. Streptomycin was used in some drug combination in the cases that recovered.

Comment. The results obtained by the use of sulfonamides and streptomycin alone or in various combinations are in striking contrast to those obtained in the days before specific therapy. Julianelle[3], summarizing a large number of studies, found an average mortality of 82%, and Feder[1], in a previous report on this subject from the Pennsylvania Hospital covering the years 1927-1938, found a mortality rate of 75% in 12 cases of acute Friedländer's pneumonia and 50% mortality in 4 chronic cases. The excellent results obtained with sulfonamides alone stand in marked opposition to the uniformly bad results obtained with penicillin alone. Unfortunately no case received streptomycin alone, but it is to be noted that the 3 cases in which it was used recovered and that in 2 of these the other part of the combination was penicillin which alone is useless.

Table 4, showing an upward trend in mortality in the later years of this series, indicts penicillin. Apparently in the sulfonamide days, the pneumonia, whether pneumococcal or Friedländer, was receiving adequate treatment from the onset of therapy, while in later years with penicillin being used primarily and generously, those patients with Friedländer's infections suffered from a fatal time lag of appropriate treatment until their sputum cultures were reported. It may be that the use of penicillin is actually harmful in Friedländer's pneumonia. However, it is clear that rapid and accurate specific diagnosis so that the proper therapy can be given is of prime importance to successful treatment.

One wonders why all the patients who received only penicillin died, for certainly 20 to 25% recovered in the days before specific therapy[1,3]. Possibly it is a coincidence due to the small number of cases. However, it is interesting to speculate upon other possible reasons. Does the penicillin perhaps kill off susceptible non-pathogens in the respiratory tract that may in themselves be somewhat antibiotic for the Friedländer bacillus? Or is the balance of nature so upset by the removal of certain susceptible populations in the respiratory tract that the Friedländer organism grows wildly without obstruction, just as certain animal populations in the world serve to maintain a check upon the multiplication of others? Perhaps we are seeing now a more virulent form of Friedländer's bacilli than in earlier days. Unfortunately these organisms were not broken down into specific types.

Wylie and Kirschner[6] recently have stated that the increased number of recoveries from Friedländer's pneumonia by the use of specific therapy is attended by an increase in chronicity. They found that 11 of 16 cases required surgical drainage or removal

of diseased lung tissue after the acute phase was over.

This situation has not occurred in the series of acute cases reported here. Most patients in a follow-up had roentgenograms showing that cavities, when present, had healed and that no progressive fibrosis had occurred. One patient has thickening of the pleura.

Summary. 1. Specific therapy for Friedländer's pneumonia has brought about a marked decrease in the mortality due to this disease.

2. In this series, the improved results must be credited largely to sulfonamides and in smaller measure to streptomycin.

3. Penicillin used alone has been of no value in this series in the treatment of Friedländer's pneumonia. It may even do harm.

4. Rapid and accurate diagnosis and early institution of the correct specific drugs are fundamental to successful results in treating Friedländer's pneumonia.

5. Positive blood culture indicates poor prognosis and negative blood culture indicates relatively good prognosis.

6. The use of specific drug therapy for acute Friedländer's pneumonia has not resulted in an increased incidence of chronic infection.

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OBSERVATIONS OF NORMAL AND ABNORMAL HUMAN INTESTINAL MOTOR FUNCTION *

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This is the report of a study of the intestinal movements of man as observed through ileac and colonic stomas. The technique was that in which 2 balloons mounted in tandem, an optical manometer and a photokymograph are used[12]. The group of patients studied included 24 who had ileac or colonic stomas, or both (Table 1).

General Considerations. Development of the Tandem-Balloon Technique. In 1923, Ganter[4] devised the first system of using 2 balloons mounted in tandem for recording human intestinal activity. Templeton and Lawson[15], in 1931, made the first detailed study with the tandem apparatus, utilizing the dog's colon. Adler, Atkinson and Ivy[1] reported the initial application of this technique to the human colon in 1941. The majority of investigators now employ this type of procedure.

The Modern Terminology. Templeton and Lawson[15] classified the various patterns recorded from the dog's intestine into 3 types. Type-I waves are small, frequent pulsations, rhythmical and nonpropulsive. Type-II contractions are larger, slower and potentially propulsive. Type-III waves are tonus waves surmounted by type-I and type-II patterns; propulsion, when achieved,

TABLE 1.—DISTRIBUTION OF STOMAS AND CONDITIONS NECESSITATING SURGICAL TREATMENT

Site of stoma	*Reason for surgical treatment*
Ileum	
7 males	6—chronic ulcerative colitis
3 females	1—appendiceal abscess with fecal fistula
	1—megacolon
	1—postoperative enterocutaneous fistula
	1—fat necrosis of mesentery following hemorrhagic pancreatitis
Transverse colon	
3 males	1—fat necrosis of mesentery following hemorrhagic pancreatitis
1 female	1—megacolon
	2—carcinoma of splenic flexure
Descending colon	
7 males	6—carcinoma of rectum
5 females	2—chronic ulcerative colitis
	2—carcinoma of descending colon
	1—traumatic fecal fistula of rectum
	1—pararectal abscess complicating osteomyelitis of hip

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is by virtue of the type-II configurations. The simpler forms were observed to summate in the more complex types. Adler, Atkinson, and Ivy[1,3] applied this terminology to their recordings from human beings.

THE CONCEPT OF FUNCTIONAL BOWEL SEGMENTS. In extending the earlier observations of Templeton and Lawson[15], Adler, Atkinson and Ivy[1,3] found that in the human colon two 3-cm. balloons, 7 cm. apart, simultaneously recorded different types of activity. They concluded that the bowel is composed of functional segments which cannot be described anatomically. It was observed that effective transport could not be achieved unless successive functional segments were so coordinated in their activity that a peristaltic wave could be propagated from one to the other, the two thus becoming a single integrated motor unit.

PERISTALSIS AND PAIN. Ganter and Stattmüller[5], using a balloon placed in the colonic stoma of a patient, observed a large peristaltic wave with a duration of about 40 seconds. The patient experienced severe cramplike pain during this period until the balloon was extruded, at which point the discomfort ceased. Similar occurrences have been noted by others[6,7]. Adler, Atkinson and Ivy[1,3] made the important observation during their studies with tandem balloons that a vigorous propulsive type of activity in a proximal segment coupled with an incoordinated, independent type of activity in the distal segment frequently produced cramplike distress in their patients, particularly if high tone were present in the distal segment. They stated that while dyssynergia between adjacent functional segments is normal, it may increase in various organic and functional states to produce a "dyssynergic colon." Colonic dyskinesia ("ill motion between adjacent or successive segments of the colon which functionally produces sufficient obstruction to the propulsion of contents to produce stasis and symptoms of tension and pain") they considered probably the result of extrinsic or intrinsic disturbances of coordination. It was felt that temporary or prolonged alteration of the normal colonic pattern may result in constipation, diarrhea, distention or colic.

EFFECT OF TONE ON MOTILITY. According to Ingelfinger and co-workers[8,9], there is an inverse ratio between tonus and intestinal caliber. Peristalsis in an intestine of small caliber (high tonus) cannot achieve transport because the contractions are necessarily of small amplitude. Amplitude of contraction and effective motility thus require a certain widening and relaxation between contractions, an effective diastole. It was concluded that hypermotility can occur only in the presence of low tonus. When, however, the optimal degree of dilatation for intestinal motility is exceeded, peristaltic efficiency diminishes. Finally, a degree of low tonus may be reached which precludes peristalsis.

Method of Study. The patients were studied either 1 hour after a light breakfast or 1½ hours after a light lunch. All medication was withheld for at least 6 hours preceding each recording. A continuous record of the intestinal activity was obtained for 60 to 180 minutes on each subject. Patients were repeatedly studied whenever possible.

Results. In general, our observations are in line with those of Adler, Atkinson and Ivy[1,3] (Table 2). Representative configurations of normal patterns appear in Fig. 1.

It is interesting that portions of certain of the records obtained from the ileum cannot be distinguished from some of the tracings taken from the colon. Conversely, certain tracings from the colon have an appearance that is identical with that of tracings obtained from the ileum. The normal motility patterns of the ileum and the left part of the colon overlap to a considerable extent. Thus, although

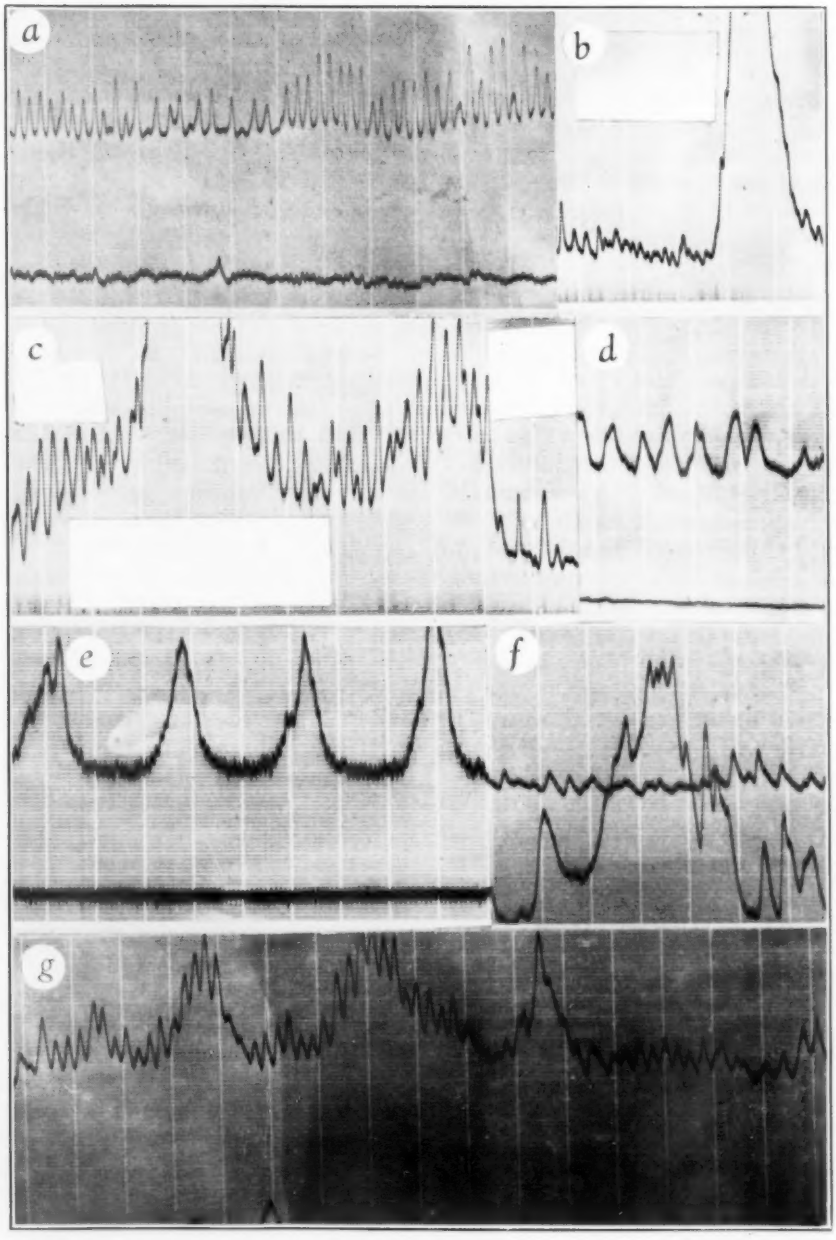

FIG. 1*a*.—Type-I contractions in the ileum. Rate here varies from 7 to 9 per minute (interval between white lines is 30 seconds). Note fluctuations in amplitude, and also tiny tonus waves in the right half of the record. *b*. Type-II contractions, ileum. *c*. Type-III contraction, ileum. Tonus wave with superimposed type-I and II waves. *d*. Type-I contractions, colon. Tandem tracing. Distal segment (lower tracing) quiescent. Rate 3 to 4 per minute. This is a less rapid rate than usual. *e*. Type-II contractions, colon. Lower tracing, respiratory control. Type-II waves are not necessarily rhythmic as here shown. *f*. Type-III contraction, colon. Tonus wave with superimposed type-I and II waves. Upper tracing, small intestine. *g*. Transitional activity, small intestine. This illustrates the manner in which basic patterns combine to produce more complex configurations. Here one may trace through pure type-I waves, type-I waves superimposed on small and large tonus waves, and finally a type-II contraction with superimposed type-I waves.

TABLE 2.—CHARACTERISTICS OF BASIC INTESTINAL MOTILITY PATTERNS

Wave type	*Rate or frequency*		*Character*
	Ileum	*Colon*	
I	5 to 12 per min.	3 to 10 per min.	Rhythmic, nonpropulsive
II	30 to 90 sec. each	45 to 120 sec. each	Occasionally rhythmic. Potentially propulsive
III	45 sec. to 15 min. each	1 to 15 min. each	Nonrhythmic. Potentially propulsive

there may be a gradient of rhythmicity between the ileum and the left part of the colon, the distinction, as evidenced by our records, is not as marked as one would expect.

THE "LAW OF THE INTESTINE." We have not recorded relaxation of a distal segment concomitant with propulsive peristalsis in the proximal segment as should be expected, were the "law" operative. In 1 recorded instance of what may have been mass peristalsis, no preliminary inhibition was observed. On 6 subjects we repeated a study made by Ganter[4], recording from one balloon while the other was overdistended to stimulate the intestine. A good motor response was obtained from the proximal segment on stimulation distally, as stated by the "law." However, contrary to the "law," proximal stimulation likewise gave a motor response distally (Fig. 2*a* and *b*.)

Carrying these observations further, we continued the study with a balloon in each limb of the double-barrel stoma of several patients. No response was elicited from either segment upon stimulation of the other. Indeed, we have never observed propagation of peristalsis across the gap of a double-barreled stoma. Each limb appears to be permanently independent of the other, once the bowel is transected.

PASSAGE OF INTESTINAL CONTENTS. Liquid feces were expelled in the presence of type-I, II or III waves, and even during intervals of virtual quiet. Whether the latter is the result of activity of the mucous membrane, which could not be recorded, or due to peristalsis higher up forcing the liquid through, cannot be said. It is important to note that during relative quiet, or with type-I waves, liquid stool simply welled from the outlet. Only in the presence of type-II or III contractions was there actual expulsion

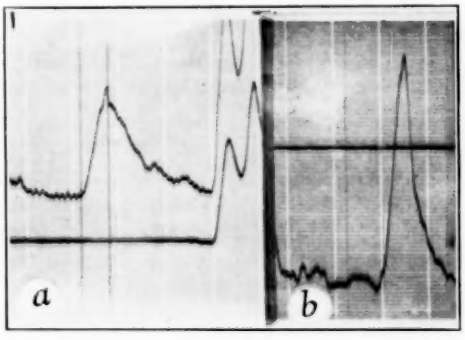

FIG. 2.—The "law of the intestine." *a*. Small intestine, tandem tracing. Distal balloon (lower tracing) was overdistended between vertical dark lines to stimulate motility. Note prompt response of proximal segment (upper tracing). *b*. Descending colon, tandem tracing. Proximal balloon overdistended at vertical dark line. Note stimulation of distal segment (lower tracing) (see text).

of the liquid with an evident degree of force behind it. Flatus seems to be handled much as liquid stool. The tandem apparatus and solid feces were extruded only by type-II and III contractions.

THE GASTROCOLIC REFLEX. Two patients with colonic stomas and 1 patient with an ileac stoma were studied immediately before and immediately after a light breakfast. In 1 patient with a colonic stoma and in the subject with the ileac stoma, a normal type of activity was present before the meal. After eating, motility was definitely diminished for at least an hour, after which the recordings were discontinued. In the second patient with the colonic stoma, violently active peristalsis was present just prior to eating, so violent that the tandem apparatus could not be maintained within the bowel for a sufficient period to obtain a suitable control record. Immediately after the meal, the apparatus could be inserted with ease. Absolute quiescence was found. No activity was recorded for a period of 90 minutes, at which time the recording was stopped. In all 3 subjects, auscultation revealed a noisy abdomen postprandially. Each patient had been studied so often that he had come to have an acute "peristaltic sense" in that he was able to appreciate subjectively movements of the bowel. After eating, each stated that peristalsis seemed to be very active in the middle and upper parts of the abdomen. Evidently motility was present in the more proximal portions of the small intestine. We must conclude that the gastrocolic reflex was not conclusively demonstrated in these patients.

DEFECATION. One patient possessed a loop-type stoma of the proximal part of the sigmoid colon and an intact rectum. From the distal limb we were able to record movements which evidently were those of defecation. The segments became coordinated in a vigorous propulsive type of activity and the patient immediately volunteered that he had a marked urge to defecate for the first time since his colostomy several months previously. He noted that his anus seemed to be drawn proximally. Inspection revealed marked tension of the intact musculature on the posterior wall of the loop with partial approximation of the 2 stomas. The tandem system was propelled caudad by the bowel, with subjective easing of the defecation impulse. Manual restraint of the recording device induced an uncomfortable urge to stool. With the subsidence of the motor activity and the reappearance of segmental independence, the urge passed away, there was relaxation of the musculature of the loop, and the patient stated that the tension on the anus had disappeared.

RETROTRANSPORT. We have observed several times, at the end of a particularly powerful coordinated contraction, a relaxation of the bowel that was more sudden than that usually seen. The tandem apparatus was quickly drawn proximally into the intestine for 5 to 6 cm. with a sucking noise. It appears likely that this phenomenon is due to the negative pressure created by the increased diameter of the bowel accompanying relaxation. This may be the same mechanism mentioned by Alvarez[2] as being responsible for the retrograde transport of fecal material from the rectum into the more proximal portions of the colon when the defecation impulse is unheeded.

SLEEP. In the quiet, dark recording room we have had frequent opportunity to observe bowel action during sleep. We have not seen any change in the recordings from either the small or large intestine during this state.

MOTILITY OF DISUSE. We have found that the motility of unused limbs of double-barrel colonic stomas is reduced both in amplitude and frequency

from that seen in the proximal limbs. Type-I waves appear very infrequently. However, after these portions are studied 2 or 3 times the activity increases, type-I waves reappear, and the recorded motility approximates normal. This finding is in accord with the observation of Quigley, Highstone, and Ivy[14] that unused segments of the bowel in the dog are potentially capable of normal motility.

Dissociation of Small and Large Intestine. One patient possessed both an ileac and a colonic stoma. By recording simultaneously from both the ileum and the transverse colon it was seen that although rhythmic contractions would appear in each at the same time, at no time did the ileum exhibit propulsive activity during such motility of the colon. The converse was also true. These findings were invariably noted during the 2 weeks in which we studied this patient. Whether this is merely coincidence or represents a normal state of affairs cannot be said. It is interesting that Puestow[13] reported similar findings in his patient.

The Effect of Tone on Motility. There appears to be an inverse relation between the amount of tonus and the effectiveness of a peristaltic wave, the more efficient contractions appearing on moderately low prevailing tonus. Fig. 3 shows an example of excessive tonus precluding effective peristalsis. In this study, obtained from the ileum, motility of the proximal segment was markedly reduced in both amplitude and frequency for nearly an hour, while the distal segment exhibited a type-II pattern of good amplitude. As illustrated, there was a sudden drop in the tone of the proximal segment from a high to a moderate level, with the immediate appearance of vigorous type-II motility.

Intersegmental Coordination. The tandem apparatus revealed that the intestine usually showed differing types of activity at the site of each balloon (Fig. 4*a*). The adjacent functional segments in which the 2 balloons were situated appeared to be entirely independent of one another most of the time.

In an effort to ascertain the approximate size of the functional segments, tandem units were assembled with the balloons 3 cm. and 5 cm. apart, in addition to the standard with the balloons 7 cm. apart. It was found that in the small intestine the functional units appeared to overlap with the balloons 3 cm. apart, but maintained their independence with the 5-cm. tandem. In the colon, the point of the overlap appeared to lie between 5 cm. and 7

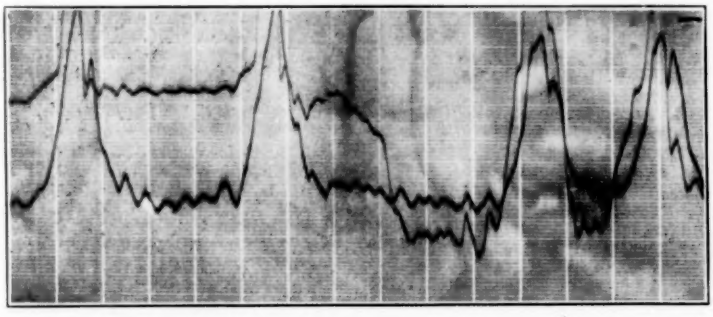

Fig. 3.—Excessive tonus precluding effective peristalsis. Small intestine, tandem tracing. Proximal segment (upper) had been quiescent nearly an hour while the distal segment showed type-II contractions. Note that with marked drop in tone in the proximal segment there immediately appears type-II motility of large amplitude.

cm. It seems that the functional segments are smaller in the ileum than in the colon.

Transport from the proximal into the distal segment was not observed to occur unless the motilities of the 2 units became coordinated in a propulsive type of activity, the 2 working together, in phase, as a single motor unit. Without this integration there was no transport, no matter how vigorous the activity of the proximal segment. With intersegmental coordination, propulsion invariably took place if the activity was vigorous (Fig. 4*b* and *c*).

Although much of the propulsive activity may be of a purely local nature, the importance of the physiologic block exerted by each functional segment on its immediately proximal neighbor through the process of intersegmental incoordination must be considerable to prevent the too rapid aboral transport of material down the intestinal tract. This mechanism is exemplified by the functional segment lying just proximal to a stomal outlet. If one records with the distal balloon lying within this area, one notes that no matter what the activity of the proximal segment, if vigorous propulsive activity is manifest by this distal segment, the balloon it contains is almost always extruded. Since there is no inhibiting functional segment distal to this portion, it may transport its contents at will. This observation clearly demonstrates the importance of normal segmental incoordination in exerting a "braking" action on the transport of intestinal contents.

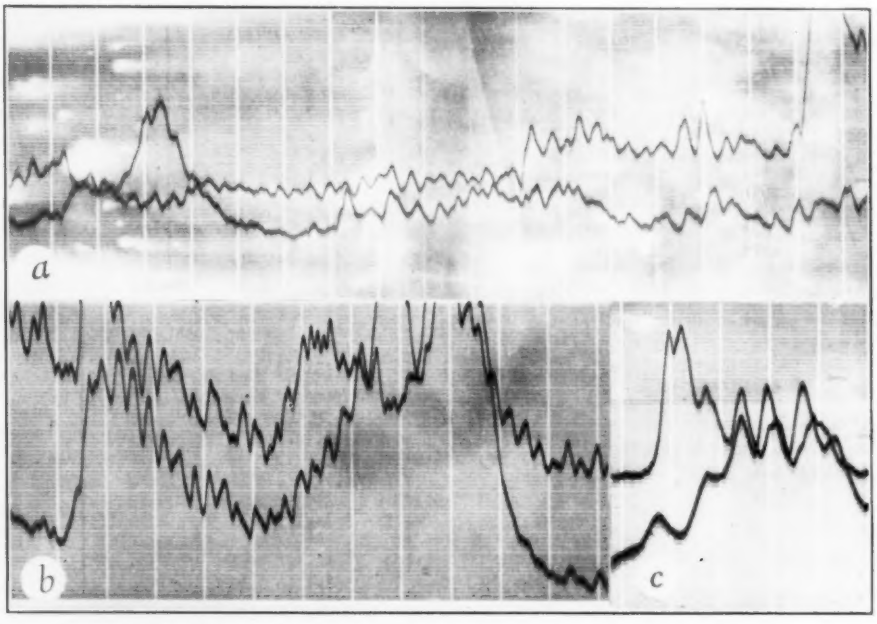

FIG. 4*a*. Typical record from the ileum. Note complete segmental independence, each showing different types of motility. *b*. Intersegmental coordination, ileum. Type-III waves. Coordination was present at first and last type-II contractions, at which times propulsion of intestinal contents took place. Note that the 2 segments fall into exact phase. *c*. Intersegmental coordination, colon. Type-III contractions. Feces extruded during period of coordination. Note that the 2 segments are exactly integrated.

INTERSEGMENTAL COORDINATION AND CHRONIC ULCERATIVE COLITIS. Two patients were studied who had colonic stomas made because of chronic ulcerative colitis. Unfortunately, the operations had been performed in areas of active disease. Typical recordings from the intestines of these persons are shown in Fig. 5*a* and *b*. At all times, a complete intersegmental coordination was observed. At no time was the normal intersegmental blocking mechanism apparent. As would be expected, there was virtually an incessant discharge of material from these stomas. Another important feature is the almost complete absence of pure type-I contractions and the complete absence of type-III configurations. The single dominant pattern was type II; it was rhythmic, but not absolutely regular. Peaks were reached every 2½ to 4½ minutes. There was abnormal, excessive and constant hypermotility. No intervals of quiet or even relative quiet appeared on the records.

These findings suggest that the diarrhea in these 2 cases of chronic ulcerative colitis was due to a motor disturbance, namely, excessive intersegmental coordination with deficient or absent physiologic blocking in the

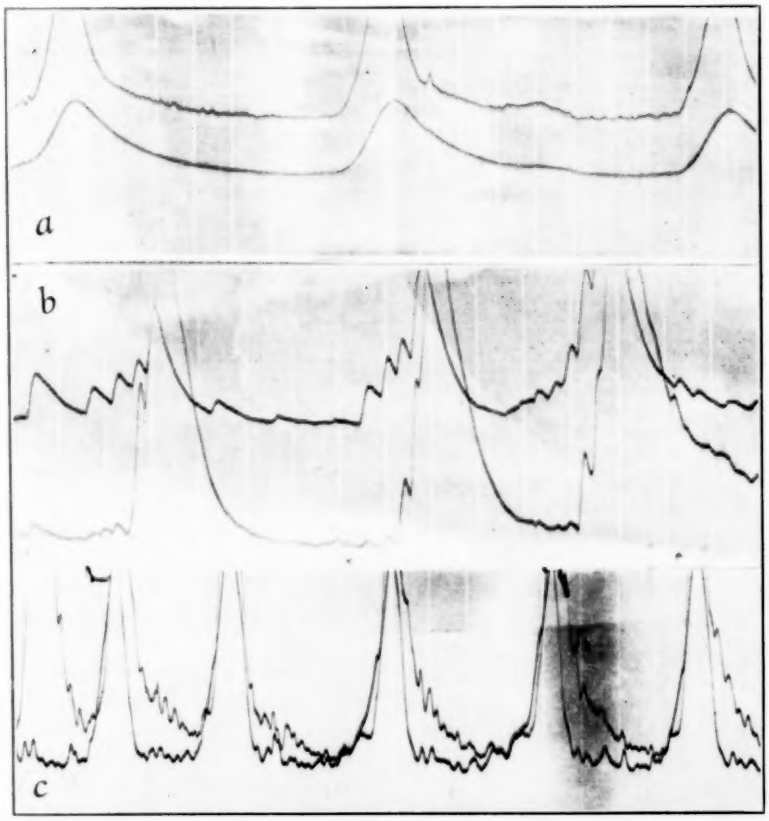

FIG. 5*a*. Chronic ulcerative colitis. Note complete intersegmental coordination, constant hypermotility, and absence of type-I and III waves. *b*. Chronic ulcerative colitis (second patient). Complete intersegmental coordination, absence of type-III waves. Type-I wave seen only superimposed on type-II contractions. *c*. Ileac motility of intestine of second patient 3 weeks after ileostomy. Note marked resemblance to the preoperative colon pattern.

face of constant hypermotility. Since only a small portion of each intestine could be studied because of limitations of the technique, further studies will be necessary to determine if this phenomenon occurs in other patients and in other portions of a bowel involved by this disease.

It is of interest that 1 of these 2 patients, studied via the ileac stoma following colectomy, demonstrated the above described motor disturbance in the small bowel as well (Fig. 5*c*). This disturbance persisted for several weeks and tended to recur even after normal intersegmental incoordination appeared, producing a diarrhea which was most difficult to control. There was no radiologic evidence of disease in the small bowel. Similar observations were obtained from other patients after ileostomy for chronic ulcerative colitis. These extreme findings were not evidenced by patients upon whom ileostomy had been performed for other conditions.

INTERSEGMENTAL INCOORDINATION (DYSSYNERGIA) AND PAIN. We have repeatedly observed that inordinate intersegmental incoordination produces discomfort in our patients. This dyssynergia appeared most frequently during intervals of increased motor activity. The proximal segment typically would develop vigorous type-II and type-III contractions, while the distal segment would appear unaffected by this effort, maintaining its independence. The tonus in the distal segment was often moderately high, but not invariably so. Within a matter of seconds, if the incoordination persisted, the patient would complain of cramplike pains localized to the region of the stoma.

The maxima of the cramps coincided with the peaks of the propulsive wave patterns recorded from the proximal segment. The discomfort persisted until the 2 segments became coordinated, with transport following, or until the vigorous activity subsided in the proximal segment.

One may induce the symptoms easily. If intersegmental coordination has taken place and propulsion is sufficient to extrude the tandem apparatus, one may manually maintain the appliance in the bowel; cramplike distress is almost invariably experienced by the patient. Thus by placing an obstruction to transport (in effect a distal incoordinated segment) discomfort may be produced.

Comment. It is apparent that intestinal motor function is a complex form of activity made up of 3 basic components: tone, motility of the various types, and the intersegmental relationships, including coordination and incoordination. In addition, it is possible that the transport of intestinal contents may be further influenced by the presence of pressure gradient developing along the intestinal tract, as well as by activity of the intestinal mucous membrane. The variety of balances which may be achieved between these factors assures a rich diversity of action on the part of the intestine.

One may safely regard tone as the general background upon which the various types of motility are superimposed. Tone has a limiting effect upon motility; at very high and very low levels of tonus, motility is seriously impaired, if not completely inhibited. Motility thus is maximally effective only when occurring on moderate tonus.

We feel that type-I configurations represent segmentation and pendulum activity in the small intestine and haustral activity in the colon. These contractions are no doubt intensified by the presence of the balloons; they may conceivably be initiated by the tandem system. Whether such activity differs markedly from that occurring in a bowel that contains foodstuff

and fecal material is a debatable point. Evidence has been presented elsewhere which suggests that rhythmic activity is principally neurogenic in origin[10].

Patterns of types II and III are, in our opinion, produced by potentially propulsive contractions which may be of a local nature or which may be propagated by means of intersegmental coordination. The fact that these configurations are summations of more simple types of activity suggests that mechanisms exist which are capable of transforming basic contractions into traveling and propelling waves. Further, the propagative ability is destroyed between the limbs of a transected bowel. Such functions must reside within the myenteric nervous system.

It is unlikely that spasm produces the majority of abdominal complaints so interpreted. Excessive intersegmental incoordination (dyssynergia) is more likely the prime factor at fault. It is not logical that generalized spasm of the intestine should produce or accompany diarrhea. As we have seen, the motility pattern is reduced in amplitude and frequency in the face of persistent high tonus. A more likely result, in such a state, would be constipation from slowed intestinal transit.

It is possible that excessive intersegmental incoordination may be the result of 2 different mechanisms. Primary dyssynergia may occur from disturbances of the coordinating mechanisms as suggested by Adler, Atkinson and Ivy[1]. Secondary dyssynergia may take place in instances of hypermotility. Here the normal incoordination may remain operative, and produce an abrupt interruption to the rapidly progressing contractions. Dyssynergia and discomfort are thus produced.

Since abdominal cramping is a major complaint among patients with chronic ulcerative colitis, and since excessive intersegmental incoordination produces these sensations, it is puzzling that dyssynergia was not recorded in the 2 patients who had this disease. Each had a long-standing illness. Although cramping had been severe in the past, neither complained of excessive discomfort during hospitalization or while being studied. Only further investigation can provide the answer to this problem. Possibly with the passage of time the blocking mechanism had become progressively exhausted in these 2 patients, much as a reversed segment of bowel, with time, can lose its normal polarity and transport material in a direction which, for it, is abnormal. The diarrhea thus continued, even though cramping ceased.

It is safe to conclude that the intestinal tract is heir to a variety of motor derangements which are only dimly perceived and generally unappreciated. Until these abnormalities are brought to light in various functional and organic conditions, therapeusis will continue to rest upon the insecure background of "spasmolysis." It has recently been pointed out that the majority of so-called antispasmodics are ineffective when administered orally and that the rationale for their administration should be seriously questioned[11].

It should be emphasized that while stress has been laid on a motor approach to intestinal dysfunction, there are accompanying alterations in circulation, absorption, excretion and secretion which in themselves may suffice to produce many of the symptoms which occur. One factor may not be emphasized to the exclusion of any of the others. It is through a combination of all of these various functions that the picture is produced; hence all must be considered if a more nearly complete understanding is to be obtained.

Summary and Conclusions. Intestinal motor function is a complex form of activity made up of 3 basic components: tone, motility of various types, and the intersegmental relationships including coordination and incoordination. Tone provides the general background upon which motility is superimposed. It is possible for excessive tone markedly to inhibit motility. A nomenclature, described by others, has been found to apply equally well to motility patterns obtained from the small and large intestine. The intestinal tract is composed of functional segments, smaller in the ileum than the colon, which usually behave independently of one another. This normal intersegmental incoordination is of prime importance in acting as a physiologic "brake" to prevent the too rapid aboral progression of intestinal contents. The intestine cannot transport its contents unless adjacent functional segments become coordinated to act together, in phase, as single motor units. Excessive intersegmental coordination has been recorded from both the colon and the ileum of patients with chronic ulcerative colitis. Excessive intersegmental incoordination produces cramping and discomfort.

It was not possible to confirm the "law of the intestine" completely; ascending and descending excitations from a point of stimulation were constantly observed in 6 patients. The gastrocolic reflex was not conclusively demonstrated in 3 patients. No alteration of motility patterns was observed during sleep. Conduction of motility was not observed to cross the transected bowel. A dissociation of activity between the small and large intestine was noted in 1 patient. The motility of defecation has been recorded and retrotransport has been described. Unused segments of the bowel are potentially capable of normal motility.

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THE USE OF POTASSIUM CHLORIDE IN THE PRE-OPERATIVE TREATMENT OF PYLORIC STENOSIS IN INFANTS

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Previous reports from this laboratory have defined certain biochemical changes occurring in infants during treatment and convalescence following the protracted vomiting of pyloric stenosis[6,7,9]. In addition to the hypochloremia, the high serum CO_2 content and the occasional azotemia long known to occur as a result of an extensive loss of gastric secretions[17,18,20], these infants developed hypokalemia and at times urine:plasma potassium ratios less than unity during a pre-operative fluid regimen which contained very little potassium[25]. Balance data indicated that with the resumption of an oral intake post operatively potassium and other constituents of milk formulae were retained in the body with a return of serum and urine potassium concentrations to values seen in healthy infants. These findings pointed to the probability that deficits of certain extracellular and cellular components incurred during vomiting, starvation and dehydration were being cancelled. In a second series of studies, herein reported, the fates of solutions of KCl and NaCl injected prior to operation have been described together with other changes in body fluids during parenteral and oral therapy.

Materials and Methods. Six infants, ultimately proven at operation to have pyloric stenosis, were admitted in the 2nd to the 11th week of life with histories of repeated vomiting. During the pre-operative period, but not necessarily on the 1st day of the study, all of the patients were given intravenously a 35 milliequivalent per liter solution of potassium chloride in 5% glucose, resulting in intakes of potassium as high as 46 mEq. Four of the 6 infants received plasma or whole blood as well. The remainder of the intake during the pre-operative period was limited to parenteral fluids in measured amounts consisting of aqueous solutions of glucose, 5 or 10%, and of sodium chloride, 0.9%. Following operation an oral intake of milk formulae was resumed. All output, including urine, stools and vomitus, was measured and analyzed for nitrogen and electrolytes. This balance technique was continued up to, and at times during and following the operative procedure. The algebraic formulae and the underlying assumptions needed in the estimation of the external and internal exchanges of the constituents of the body and of the therapeutic regimen have been described in publications from this and other laboratories[10,12,14,15]. The results are presented in the tables and figures.

Results. A. External Balances. The electrolyte data in Figs. 1 and 2 point to a considerable retention of

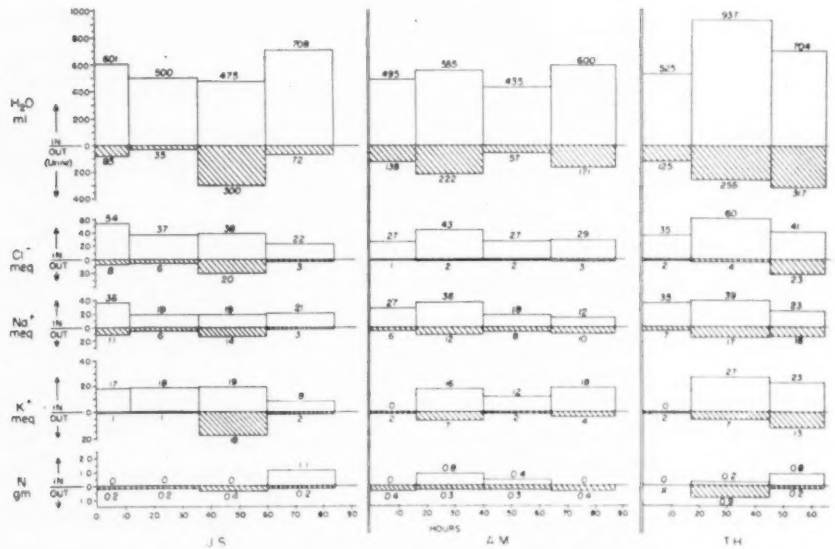

FIG. 1.—Intake of water, output of urine, and complete external balances of electrolytes and nitrogen in 3 infants operated at 42, 87, and 43 hours, respectively, following start of the balance studies. It is evident from the relative magnitudes of the intake and output (see figures above and below rectangles) that considerable proportions of the administered potassium, sodium, and chloride were retained in the body. It is to be noted that this occurred even during periods characterized by negative balance of nitrogen.

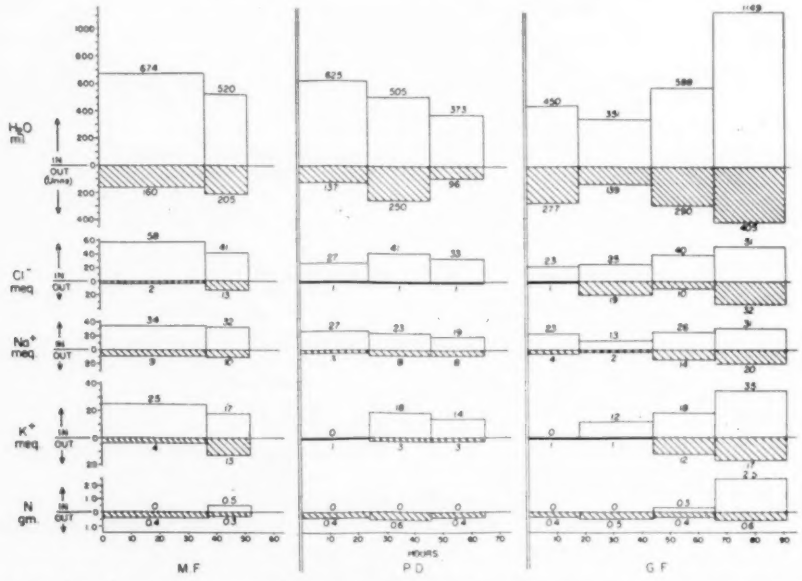

FIG. 2.—Intake of water, output of urine and complete external balances of electrolytes and nitrogen in 3 infants operated at 39, 70, and 46 hours respectively after the start of the balance studies. As in Fig. 1 it is clear from the external balances in these patients, that administration of potassium, sodium, and chloride permitted a significant retention of these electrolytes within the body irrespective of the absence of a protein intake. The balances of body water in these and the preceding 3 infants are discussed in the text.

administered potassium, sodium, and chloride during recovery from vomiting. This is clearly illustrated by the relative magnitudes of the intake and output of these various ions plotted above and below the horizontal lines, respectively. The validity of these findings is supported by the uniformity with which positive balances were recorded not only from patient to patient but also in successive periods in any one patient. When the potassium exchanges are computed on a cumulative basis over the entire length of each experiment, retention of this electrolyte varied between 7 and 12 mEq. per kg. of initial body weight. Similarly, the positive balances of sodium extended from 14 to 19 mEq. per kg. The highest values were observed however in the case of chloride, since the body stores of this anion were increased by 27 to 32 mEq. per kg. It will be recalled that the amounts of chloride ion which were given of necessity exceeded, in view of the salts used, the intake of either of the associated cations.

In contrast to the consistently positive balances of electrolytes, the exchanges of nitrogen indicated losses in the earlier periods followed by retention in succeeding intervals (Figs. 1 and 2). This pattern reflected the absence of protein intake in the early periods and the introduction of milk formulae in the later periods, respectively. The glucose administered during this same time only averaged 5 to 11 gm. per kg. per day. Finally, comparison of the water intake and the urine volume in the individual periods indicates that the former was invariably the greater. This does not by itself provide an accurate index of water balance because losses via the skin and lungs were not measured. The progressive rises in body weight recorded during times of low food intake are only explainable, however, by a retention of fluids.

B. Balances of Extracellular and Cellular Constituents. From Table 1 it is evident that the total amounts of extracellular potassium, in a cumulative summary in each patient, increased only slightly, that is by 6 mEq. or less. This contrasts sharply of course with the marked rises in extracellular sodium, reaching as high as 117 mEq. when evaluated on the same basis. This retention of administered sodium together with chloride and water was uniformly associated with a progressive expansion in the volume of the extracellular fluid. The final volumes varied between 28 and 38% of the body weight assuming, in accordance with the usual procedure for the calculation of changes in the chloride space in dehydrated subjects, an initial volume of 15%. This indicates a restoration of this fluid compartment to proportions characteristic of healthy infants[21]; edema did not appear in any of the subjects.

There is a convincing uniformity in the intracellular balances of the electrolytes studied. With but 2 exceptions (Patients A. M. and G. F.), the total amounts of intracellular potassium increased while the sodium supplies in cells diminished (final 2 columns, Table 1). These 2 isolated negative balances of potassium were inevitable, since during these periods potassium was not given. The general pattern of cell cation balances suggests that the entry of potassium into cells was probably associated with a movement of sodium out of cells. The exchanges of these 2 cations were not always of the same order of magnitude. This has been noted and discussed in reports of previous studies[10,19]. Finally, in view of the frequency of negative balances of cell nitrogen, it necessarily follows that potassium was usually retained in cells despite a catabolism of cell pro-

tein which would tend to release cell potassium[14]. In the isolated instances in which cell nitrogen increased, the retention of potassium by cells always exceeded in magnitude the positive balances to be expected with the presumed formation of intracellular protein.

C. Alterations in Blood and Serum Constituents (Table 2). Serum potassium levels were either normal, slightly elevated, or low prior to the start of the individual studies, using values seen in healthy infants as standard[8,21]. This variability presumably represents the end-result of the interaction of the numerous factors which influence serum potassium values. These have been discussed in considerable detail elsewhere[5]. It should be noted that at the end of each study all infants had normal serum potassium levels. In the 5 studies in which initial blood non-protein nitrogen values are available, subsequent decreases are recorded down to or within the range of normal. Insofar as such changes represented clearance of non-protein nitrogen constituents, corrections have been made for this fraction in the net cell balances of nitrogen. These can be readily calculated by comparison of the net cell nitrogen balances in Table 1 with the external balances in Figs. 1 and 2. All but Patient G. F. showed at the beginning of the study the characteristic hypochloremia and elevated serum CO_2 content following upon prolonged vomiting. There is no ready explanation for the one exception. This infant was greatly malnourished. It is possible that starvation and dehydration had cancelled an earlier rise in bicarbonate and hypochloremia. In the other 5 patients treatment with water, glucose and the chloride salts raised chloride levels to normal while the CO_2 content de-

TABLE 1.—BALANCES OF EXTRACELLULAR AND CELLULAR CONSTITUENTS IN 6 INFANTS WITH PYLORIC STENOSIS UNDER KCl AND NaCl ADMINISTRATION

	Time from start of treatment	*Extracellular Balance*			*Intracellular Balance*		
		Fluid	*Na*	*K*	*N**	*Na*	*K†*
Patient	*hours*	*L.*	*m.Eq.*	*m.Eq.*	*gm.*	*m.Eq.*	*m.Eq.*
J. S.	0–12	+0.3	+42	+3	0	−17	+14
	12–36	+0.2	+38	+2	−0.2	−25	+16
	36–60	+0.2	+13	+1	−0.4	−8	+1
	60–84	+0.1	+20	−1	+0.8	−2	+5
A. M.	0–16	+0.2		0	−0.2		−2
	16–40	+0.3		+2	+0.7		+5
	40–64	+0.1		+2	−0.1		+9
	64–87	+0.2		+2	−0.2		+12
T. H.	0–17	+0.3					
	17–45	+0.4	+63	+4	−0.4	−41	+16
	45–65	+0.1	+8	−1	+0.7	−1	+9
M. F.	0–37	+0.5		+3	−0.1		+18
	37–61	+0.3	+47	+2	+0.1	−25	+2
P. D.	0–24	+0.2			−0.1		
	24–48	+0.2	+32	+1	−0.5	−17	+15
	48–65	+0.2	+18	+1	−0.2	−7	+10
G. F.	0–18	+0.2	+27	+1	−0.4	−8	−1
	18–44	+0.1	+16	0	−0.6	−5	+12
	44–66	+0.2	+34	+2	−0.1	−22	+4
	66–91	+0.3	+40	+2	+1.9	−29	+12

* Alterations in blood NPN have been taken into account in the calculation of the net cell N balances.
† Represent changes in excess of those associated with N metabolism (1 g. N = 2.38 m.Eq. K).

clined. It is to be noted that hyponatremia was conspicuous by its absence prior to treatment, and that only fluctuations within a narrow range were seen during the periods of sodium salt administration.

Discussion. The observations presented in this paper indicate that during the recovery phases following the vomiting of pyloric stenosis, the infant retains considerable amounts of administered potassium together with sodium, chloride, and water, even when the caloric and nitrogen intakes are limited. These positive balances can be reasonably taken to represent a cancellation of previously incurred deficits. Their uniform character and their persistence support such a point of view. The presence of normal serum potassium values at the end of each study, the reexpansion of the extracellular space with water, sodium, and chloride without hypernatremia or hypochloremia, and the displacement of sodium from cells by entering potassium are all consistent with this interpretation. Comparable changes have been reported from this and other laboratories in diabetic acidosis, in diarrhea of infancy, and in adult gastro-intestinal diseases characterized by starvation and dehydration[2,10,12,13,16,19,22,24,28,29].

It is of some interest to draw certain comparisons between these infants who were given potassium chloride prior to operation and a preceding group[6] maintained on potassium-free fluids during the same interval. Positive

TABLE 2.—ALTERATIONS IN BLOOD AND SERUM CONSTITUENTS IN 6 INFANTS WITH PYLORIC STENOSIS UNDER KCl AND NaCl ADMINISTRATION

			Concentrations				
			Blood	*Serum*			
Patient *Age-Sex*	*Time from start of treatment* *hours*	*Body weight* *Kg.*	*NPN* *mg./100 cc.*	*HCO_3* *m.Eq./L*	*Cl* *m.Eq./L*	*Na* *m.Eq./L*	*K* *m.Eq./L*
J. S.	0	3.82	31	31.2	83.8	138	3.7
5 wk. M	12		22	23.2	97.4	139	5.2
	36	4.05		21.4	103.8	148	5.6
	60	4.05	21	23.9	99.4	135	5.7
	84	4.14	24	24.3	103.1	139	4.8
A. M.	0	4.00	40	33.1	76.8		3.7
11 wk. M	16	4.08	31	31.4	85.6		2.6
	40	4.19	22	25.4	98.0		3.9
	64	4.25	30	21.4	103.1		4.8
	87	4.47	23	22.2	109.8	148	5.5
T. H.	0	3.30	55	31.1	84.3		
5 wk. M	17	3.55	33	25.8	94.3	142	3.7
	45	3.55	22	24.6	105.4	147	5.8
	65	3.60	20	25.4	102.6	142	4.6
M. F.	0	2.87	43	30.8	83.7		6.5
2 wk. F	37		26	26.4	94.8	144	5.7
	61		29	23.2	95.5	147	5.6
P. D.	0	3.66	45	30.9	75.1		
6 wk. M	24	3.78	32	34.5	79.0	142	3.4
	48	3.83	30	28.3	96.0	146	3.5
	65	3.83	22	28.8	97.2	137	4.9
G. F.	0	2.84		21.7	101.6	136	6.0
6 wk. M	18	2.87	21	20.7	107.0	136	5.3
	44	2.93	25	13.6	98.2	139	5.0
	66	3.04		17.5	103.5	145	6.2
	91	3.06	28	20.1	97.6	142	5.9

balances of intracellular potassium were recorded much earlier in those receiving KCl. This was associated with a cancellation of the trend toward hypokalemia and urine-plasma potassium ratios of less than 1.0 seen during the pre-operative period in the infants not receiving the potassium salt pre-operatively. As might be expected in view of the use of saline solutions in both groups, pre-operative re-expansion of extracellular fluid volume was observed with comparable frequency. In view of the limited number of cases no statement is possible as to whether the absence or presence of KCl in early treatment influenced the clinical status. This fact is, however, certainly clear: the use of KCl resulted in the early appearance of biochemical changes seen *after* resumption of oral feedings post-operatively in the non-KCl group. Since these changes, namely retention of potassium together with the return of normal ranges of serum and urine values for this electrolyte, are characteristic of restoration of body fluid composition to normal, their accelerated return is of course highly desirable.

The practical aspects of replacement therapy in infants after vomiting can be discussed briefly in view of the detailed descriptions already given of the fate of administered solutions and solutes. Such patients should receive water, sodium and chloride to replace previous losses of extracellular fluid and thereby obviate circulatory inadequacy. The impairment of cardiovascular efficiency may often be of sufficient degree however to necessitate the early use of blood or plasma as well. Glucose should be given to supply calories, probably in amounts greater than those used in our patients. The administration of potassium chloride solution permits the replenishment of extracellular and cellular potassium, and provides the chloride ion in excess of sodium. The latter is desirable in view of the greater losses of chloride than of sodium in gastric secretions.

Which solutions should be used for this purpose and in what concentrations? It has been established that renal function in the young infant is immature[1,26,27]. Hence sodium chloride should be administered in amounts which will ultimately provide a hypotonic rather than an isotonic increment to the body fluids. In view of the hyposthenuria in infants the excess of water can then be used to advantage for renal excretory purposes. If 0.9% saline is employed, it should be diluted with sufficient volumes of a solution of glucose in water. A 5% solution of the latter is to be preferred to higher concentrations in view of their diuretic and dehydrating effects. Insofar as potassium salts are concerned, we have preferred to administer slowly a relatively dilute mixture, 35 mEq. per l. in 5% glucose, following the establishment of adequate renal function and a good urine flow. This precaution is dictated by the known toxic effects of increased extracellular concentrations of potassium which include electrocardiographic alterations, culminating in cardiac standstill, and possible skin and neurological manifestations[5,12,23].

There are available several premixed solutions which take many of these factors into account and therefore suffice to meet the needs of many clinical situations[3,4,11]. When possible, however, individualized prescriptions are to be preferred, since they permit control of the sequence as well as the quantity of replacement therapy.

Summary and Conclusions. Measurement of external and internal exchanges following injection of potassium and sodium chloride solutions together with glucose to 6 infants convalescent from vomiting of pyloric

stenosis revealed a retention of administered potassium, chiefly in the cells, and of sodium and chloride in the extracellular fluid.

The therapeutic implications of these changes (such as the substances and their concentrations which should be given and pre-mixed versus individualized solutions) have been briefly discussed.

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LIVER BIOPSY: CORRELATION WITH CLINICAL AND BIOCHEMICAL OBSERVATIONS

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Although needle biopsy of the liver is not a new procedure[20], increasing interest in its use as an adjunct to the clinical and laboratory evaluation of the patient with hepatic or suspected hepatic disease has been demonstrated. The present report comprises 82 biopsies performed upon 66 selected patients with hepatic or suspected hepatic parenchymatous disease, and 16 subjects without clinical evidence of disease who served as normal controls. This latter group seems to be particularly relevant to the problem of the proper evaluation of this procedure. An attempt has herein been made to correlate the histopathological findings with the clinical and biochemical findings. For purposes of evaluation the patients have been divided into 7 groups according to their clinical diagnoses: Group I: Portal cirrhosis, 30 patients; Group II: Acute hepatitis, 3 patients; Group III: Chronic hepatitis, 10 patients; Group IV: Hepatomegaly of undetermined etiology, 12 patients; Group V: Congestive hepatomegaly, 5 patients; Group VI: Sarcoidosis, 6 patients; Group VII: No evidence of liver disease, who served as controls, 16 patients.

Technique. Originally the mid-clavicular line, subcostal approach as recommended by Baron[3], was employed, utilizing the "Vim-Silverman" needle. However, the lateral, mid-axillary, intercostal approach was later adopted[35], because of the desire to extend the technique in the elucidation of liver disorders not accompanied by marked hepatomegaly. So satisfactory has the intercostal technique proved to be that the subcostal approach has been abandoned entirely. Of approximately 200 biopsies carried out by the authors, 8 have been unsatisfactory, all but one of which were done when the anterior approach was used.

The procedure is not without resulting complications; particularly if a good technique is not strictly adhered to, and the contraindications not closely observed[3,21]. In the authors' experience, 3 patients (1.5%) have had complications incident to the biopsy. These include 1 case of subcutaneous bleeding and 1 case of minimal pneumothorax at the right base; recovery in both was rapid and uneventful. A 3rd patient (No. 56, Table 3) developed intra-abdominal bleeding 4 days following the biopsy procedure, and died during an exploratory laporotomy. Although the patient had a past medical history of several episodes of severe gastrointestinal bleeding, and a definite bleeding point was not found either at surgery or at autopsy, the mortality must be considered incident to the biopsy procedure. The immediate cause of death during surgery was acute cardiac arrest apparently secondary to severe coronary artery disease. At autopsy on both gross and microscopic examination of the liver, the biopsy site was well organized and exhibited no evidence of recent bleeding. The death of this patient emphasizes 2 contraindications to the procedure that in the opinion of the authors should always be observed; namely, abnormal bleeding tendencies (clinical and laboratory evidence), and cardiac failure.

Observations. The patients in this report were admitted to the medical wards over a 2-year period. The collected data are presented in Tables 1 to 3.

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TABLE 1.—RAW DATA: CORRELATION OF BIOCHEMICAL AND HISTOPATHOLOGICAL OBSERVATIONS WITH THE CLINICAL DIAGNOSES†

Case No.	Histopathological Diagnosis	RBC (mil)	Hg (%)	Sed. Rate (mm/hr)	Serum Proteins (gm/100 cc)	*BSP (% Ret.)	**Thymol Turbidity (units)	Icterus Index	Serum Bilirubin (mg/100 cc)	***Glucose Tolerance (decreased)
	Group I. Portal Cirrhosis (Clinically Diagnosed)									
1.	Portal cirrhosis	3.1	60	20	7.0 (3.5/3.5)	12	12	10	.8	Mildly
2.	Portal cirrhosis	3.6	80	22	6.0 (2.8/3.2)	18	14	32	2.8	Moderately
3.	Portal cirrhosis	4.2	80	36	6.7 (—)	34	2.5	9	1.2	Mildly
4.	Portal cirrhosis	2.8	65	3	5.3 (2.5/2.8)	16	22	30	—	—
5.	Portal cirrhosis	5.2	100	33	6.3 (—)	12	12.5	24	4.4	Mildly
6.	Portal cirrhosis	4.3	90	11	7.2 (4.7/2.5)	2	—	3	—	Mildly
7.	Portal cirrhosis	4.5	90	18	7.8 (4.2/3.6)	23	3.5	16	1.3	Mildly
8.	Portal cirrhosis	4.0	80	13	7.3 (4.4/2.9)	—	25	10	1.3	—
9.	Portal cirrhosis	3.5	80	38	7.6 (5.4/2.2)	14	9.5	12	1.8	Moderately
10.	Portal cirrhosis	4.8	100	—	8.8 (—)	17	0	—	—	—
11.	Portal cirrhosis	—	—	—	6.9 (—)	26	1.5	—	—	Mildly
12.	Portal cirrhosis	4.0	85	56	6.3 (2.1/4.2)	—	15.5	52	—	Moderately
13.	Portal cirrhosis	4.9	95	32	8.6 (3.5/5.1)	17	60	4	—	Markedly
14.	Portal cirrhosis	—	90	6	8.2 (5.1/3.1)	17	2	8	1.2	—
15.	Portal cirrhosis	—	—	27	7.7 (5.2/2.5)	21	7.2	6	—	Markedly
16.	Portal cirrhosis	—	90	—	7.8 (5.3/2.5)	24	3.8	24	—	Normal
17.	Portal cirrhosis	4.2	85	—	7.8 (5.3/3.5)	29	0	12	—	Mildly
18.	Portal cirrhosis	4.3	80	19	7.8 (5.2/2.6)	1	11	4	0.2	Mildly
19.	Portal cirrhosis	—	80	16	7.0 (4.3/2.7)	2	8.6	4	0.4	—
20.	Portal cirrhosis	—	100	—	7.8 (3.9/3.9)	16	6.9	4	—	—
21.	Portal cirrhosis	—	90	12	—	22	20	8	—	—
22.	Portal cirrhosis Passive congestion	4.1	90	16	6.0 (2.8/3.2)	20	12	46	10.1	Moderately
23.	Portal cirrhosis Passive congestion	3.6	68	20	6.5 (3.0/3.5)	28	14	34	7.3	Mildly
24.	Fatty metamorph., marked	—	90	30	7.4 (5.5/1.9)	29	3.5	2	—	Mildly
25.	Fatty metamorph., marked	—	100	33	7.7 (5.0/2.7)	15	2	3	0.1	—
26.	Fatty metamorph., mild	—	100	21	7.5 (4.8/2.7)	3	3	6	0.2	Mildly
27.	Fatty metamorph., marked	4.2	95	16	8.2 (6.2/2.0)	33	6	4	0.2	Mildly
28.	Fatty metamorph., mod.	4.8	95	—	7.0 (4.5/2.5)	10	1.4	4	—	Normal
29.	Fatty metamorph., marked	3.5	85	—	5.5 (3.3/2.2)	10	1	1	—	—
30.	Fatty metamorph., mod.	—	80	18	7.5 (5.5/2.0)	—	3	9	—	Mildly

* Bromsulfalein retention was measured at the end of 45 minutes, using the spectrophotometer. The patients' serum prior to dye injection was used as the control. Five Mg. of dye per kilogram of body weight was used.

** Thymol turbidity is expressed in units according to the technique of Shank and Hoagland. For this laboratory 6 units is regarded as the upper limits of normal.

*** Glucose Tolerance was expressed as mildly, moderately, or markedly decreased if the blood sugar at the end of the 2nd hour was over 120 mg. per 100 cc., but less than 180 mg.; over 180 mg., but less than 250 mg.; and over 250 mg. per 100 cc. blood, respectively. Only the results of the standard oral glucose tolerance test were utilized in this table.

† All biopsy specimens were examined histopathologically by the Department of Pathology, Brooke General Hospital, by the Army Institute of Pathology, and finally by the authors.

GROUP I. **Clinically Diagnosed Portal Cirrhosis (30 Patients). A.** CORRELATION OF CLINICAL AND HISTOPATHOLOGICAL OBSERVATIONS. The clinical diagnosis of cirrhosis was made only if a well established clinical picture was thought to exist. If hepatomegaly was accompanied only by indefinite symptoms and signs, the patient was classified as hepatomegaly of undetermined etiology (Group IV). On histological examination the liver biopsy demonstrated definite disturbance of normal lobular architecture, portal area fibrosis, and round cell infiltration in 23 of the 30 patients in this group. In addition, bile duct proliferation was usually evident on the sections, and signs of hepatic cell regeneration were frequently seen. In the remaining 7 patients fatty metamorphosis alone was observed. This was classified as mild, moderate or marked, depending upon the degree of fatty vacuolization evident on the section. The probable pathogenetic relationship of fatty liver as a result of alcoholism or dietary deficiency and as a precursor of the classic fibrotic type of cirrhosis in humans[16] as well as experimentally in animals is well known. The antecedent diet was inadequate in over

half of the patients, and poor in about one-third. The incidence of significant alcoholism amounted to 85%, which is quite high but commensurate with other previous reports[6,17]. No difference existed in the average age of the patients showing fatty metamorphosis as compared with those showing frank cirrhosis. The average age was 50 years; the youngest was 30, the oldest 68.

The liver was palpable 4 cm. or more below the costal margin in 70% of the group. This observation of the high incidence of hepatomegaly, confirmed by others[9], casts doubt upon the accuracy of connotation of the term "atrophic" cirrhosis so frequently attributed to this pathological entity. Two of these patients displayed congestive heart failure, complicating the hepatic disease.

Seven patients had a past history of jaundice, 3 of whom had a recurrence just prior to admission. Four additional patients were jaundiced for the first time upon admission. Therefore, one-third of the patients either had jaundice or a past history of jaundice.

B. Correlation of Biochemical and Histopathological Observations. In general, the 7 patients showing fatty metamorphosis revealed biochemical abnormalities similar to the 23 patients with histological evidence of unequivocal cirrhosis although the disturbances tended to be less marked.

Erythrocyte Count and Hemoglobin Determinations. Of the patients thus studied, about two-thirds presented red cell counts of 4.2 million or less. The lowest was 2.8 million. On the other hand, only one-third showed hemoglobin levels of 80% of normal or below. These findings, indicative of a significant incidence of mild anemia, are less remarkable than reported elsewhere[17].

Sedimentation Rate. This determination, using the Wintrobe method, was done on 23 patients. The average rate was 23 mm. per hour, with a maximum rate of 56 mm. per hour. Twenty-one patients had rates greater than 10 mm. per hour; in 12, the rate exceeded 20 mm. per hour.

Prothrombin Time. The prothrombin time was used to a greater extent as a check upon the safety of the biopsy procedure rather than as a function test. Therefore, patients with gross disturbances of prothrombin time are not included here, since the biopsy procedure was thought to be contraindicated. The administration of 25 to 100 mg. of vitamin K for 3 to 4 days resulted only occasionally in a reduction of the prothrombin time to a level regarded as safe for the biopsy procedure.

Serum Protein Studies. None of the patients showing only fatty metamorphosis liver changes revealed abnormal serum protein studies. However, in the patients with frank cirrhosis, of 16 serum proteins which were fractionated, 11 (69%) showed either a reduction in the serum albumin or an elevation of the serum globulin, with or without a net reduction of the total serum proteins, but with a reduction of the albumin/globulin ratio toward unity or below. Perhaps, the fact that the majority of the cases were rather well compensated may have influenced the A/G ratio toward normal in a relatively high percentage of cases, since the inverse relationship of liver cell damage with the albumin/globulin ratio has been demonstrated[15].

Bromsulfalein Retention. This liver function test was performed on 27 of the 30 patients. Twenty-three showed abnormal retention of dye, that is, 8% or more after 45 minutes. There was no significant difference between the cases of fatty metamorphosis and those having frank cirrhosis. Of the liver function tests for the detection of the hepatocellular damage associated with cirrhosis, it has been the experience of

the authors that in the usual clinical laboratory this test is the most reliable, largely because of its simplicity. A significant correlation of bromsulfalein retention with diffuse liver cell damage as demonstrated by liver biopsies has previously been shown[15].

Thymol Turbidity Test. Of the 7 patients with hepatic fatty metamorphosis, none showed gross abnormality of the thymol turbidity test, and only one was borderline. In contrast, of the patients showing frank portal fibrosis, 75% revealed abnormal tests. There seemed to be a rough correlation between the disturbance of the thymol turbidity test and the extent of hepatic fibrosis, liver cell damage, and distortion of the lobular architecture. Again, the lack of a high percentage of near terminal cases in this series may account for the lower incidence of abnormal thymol turbidity tests than has been reported by Kunkel (89%)[27] and others[14,15].

Although not tabulated, the cephalin cholesterol flocculation test was done on 24 of the cases in this group. The results very closely paralleled the abnormalities of the thymol turbidity test in those patients showing frank cirrhosis. Seventy percent were abnormal. As noted by Hanger and Patek[19], none of the 7 patients exhibiting only fatty metamorphosis showed disturbances of this test.

Icterus Index and Serum Bilirubin. Twenty-eight of the patients in this group had serial icterus index determinations. None of the patients showing only hepatic fatty metamorphosis displayed an elevation of the icterus index or serum bilirubin. Of those patients exhibiting portal fibrosis, 63% showed elevated icterus indices; and of these, 7 exhibited clinical jaundice. The

TABLE 2.—OBSERVATIONS ON PATIENTS CLINICALLY DIAGNOSED ACUTE HEPATITIS, CHRONIC HEPATITIS OR HEPATOMEGALY OF UNDETERMINED ETIOLOGY

Case No.	Histopathological Diagnosis	RBC (mil)	Hg (%)	Sed. Rate (mm/hr)	Serum Proteins (gm/100 cc)	*BSP (% Ret.)	**Thymol Turbidity (units)	Icterus Index	Serum Bilirubin (mg/100 cc)	***Glucose Tolerance (decreased)
	Group II. Acute Hepatitis (Clinically Diagnosed)									
31.	Acute hepatitis Cl. Dg.: Homol. serum	—	80	10	7.5 (4.9/2.6)	41	16	45	8.8	Normal
32.	Acute hepatitis Cl. Dg.: Syphilitic	4.6	92	22	7.1 (4.1/3.0)	—	21	42	9.0	—
33.	Acute hepatitis Cl. Dg.: Infectious	—	90	—	8.1 (4.2/3.9)	41	13.5	36	9.6	—
	Group III. Chronic Hepatitis (Clinically Diagnosed)									
34.	Normal liver	4.5	100	18	7.0 (4.0/3.0)	0	6	4	—	—
35.	Diffuse hepatitis and cholangiolitis	4.6	100	—	7.5 (5.5/2.0)	12	7.0	4	—	—
36.	Normal liver	3.8	80	15	6.5 (5.5/1.0)	9	8	4	—	Moderately
37.	Normal liver	5.3	100	3	7.5 (5.0/2.5)	1	17	6	0.1	Mildly
38.	Normal liver	4.6	100	4	9.1 (5.8/3.3)	20	10	16	— *	Flat curve
39.	Normal liver	—	95	—	—	—	0	4	—	—
40.	Chronic cholangitis, mild	4.7	90	15	8.2 (5.1/3.1)	1	5	4	0.4	Normal
41.	Chronic cholangitis, mild	—	95	2	7.4 (5.2/2.2)	1	9	6	0.6	Normal
42.	Normal liver	4.7	90	6	7.2 (4.4/2.8)	—	0	4	—	Normal
43.	Chronic cholangitis, mild	—	100	13	6.7 (4.6/2.1)	4	10	4	1.2	Mildly
	Group IV. Hepatomegaly (Undetermined Etiology)									
44.	Fatty metamorph., marked	—	85	21	7.7 (4.6/2.1)	14	1	4	—	—
45.	Normal liver	—	80	29	7.4 (4.8/2.6)	2	1.5	4	0.4	Normal
46.	Normal liver	3.6	75	60	7.0 (—)	3	—	8	—	Normal
47.	Normal liver	—	95	6	7.8 (4.0/3.8)	0	6	3	0.4	Normal
48.	Chronic cholangitis, mild	—	90	7	7.2 (4.1/3.1)	2	16.4	4	—	Normal
49.	Portal cirrhosis	4.5	95	12	7.2 (4.0/3.2)	12	10	6	0.6	Normal
50.	Normal liver	—	100	15	7.2 (4.6/2.6)	—	3	10	—	—
51.	Normal liver Cl. Dg.: Pulm. Tbc.	4.1	90	38	7.5 (3.8/3.7)	5	1.6	4	—	—
52.	Cholangitis, mild	4.0	80	8	6.2 (3.4/2.8)	3	7.5	4	0.4	Flat curve
53.	Normal liver Cl. Dg.: Pulm. Tbc.	—	100	34	7.3 (3.8/3.5)	7	6	4	—	—
54.	Normal liver	3.9	80	14	6.2 (3.3/2.9)	6	4	4	0.6	Normal
55.	Fatty metamorph.	—	90	16	7.7 (4.8/2.9)	10	8	4	—	Mildly

*, **, *** See footnotes to Table 1.

serum bilirubin exceeded 1.2 mg. per 100 cc. in 7 (47%) of 15 patients.

Glucose Tolerance Test. Twenty-one patients received glucose tolerance tests. Two had a normal glucose tolerance, while 13 demonstrated a mild decrease, 4 a moderate, and 2 a marked decrease in tolerance. No correlation could be shown to exist between the degree of fatty metamorphosis or the extent of portal fibrosis and the degree of diminished glucose tolerance[28]. However, none of the patients exhibiting only fatty metamorphosis showed gross disturbances of glucose tolerance. No instance of fasting hypoglycemia was observed, and none of the patients presented symptoms suggestive of spontaneous hypoglycemia as noted by Conn *et al.*[11].

Group II. **Infectious Hepatitis.** A. Correlation of Clinical and Histopathological Observations. The clinical diagnosis of acute hepatitis was substantiated histopathologically in each case. The histopathological evidence consisted of non-specific, hepatocellular damage with destruction, necrosis and disappearance of hepatic cells, together with an intense inflammatory cell infiltration. Despite the fact that the etiology of the hepatitis was different in each case, a specific etiological diagnosis could not be made on tissue examination alone. In the case of homologous serum jaundice (No. 31), the history of multiple blood transfusions 93 days prior to the onset of jaundice strongly suggested the etiological basis. The patient diagnosed syphilitic hepatitis (No. 32) demonstrated, in addition to an enlarged and tender liver, a skin rash suggestive of secondary syphilis, together with a generalized lymphadenopathy, and a positive serological test for syphilis (80 Kahn units, rising titer, and positive Wassermann). The patient improved, and the liver receded dramatically on a course of penicillin as outlined for syphilitic therapy. The liver biopsy showed an intense, non-specific inflammation characterized by round cell infiltration with destruction and disappearance of hepatic cells.

B. Correlation of Biochemical and Histopathological Observations. The widespread nature of the inflammatory process in these 3 patients with acute hepatitis was reflected in the laboratory data. All demonstrated elevated icterus indices with moderate increases in the serum bilirubin. All likewise showed a significant increase in the thymol turbidity tests and abnormal cephalin flocculation tests at both 24 and 48 hours. Serum proteins and routine blood studies were normal except for a tendency toward hyperglobulinemia.

Group III. **Chronic Hepatitis.** A. Correlation of Histopathological and Clinical Observations. There were 10 patients upon whom the clinical diagnosis of chronic hepatitis had been made. All gave a history of continued subjective symptoms and of recurrent jaundice following acute hepatitis 9 months to 5 years prior to the present study. *Only one patient was clinically jaundiced* at the time the liver biopsy was done.

Here a positive histopathological diagnosis was based upon the presence of an abnormal infiltration of inflammatory cells, usually lymphocytes and plasma cells, into the portal areas, with or without periportal fibrosis, but with no significant disturbance in lobular architecture. Four of the 10 patients showed histopathological abnormalities of the specimens obtained by biopsy. Three were classified as minimal chronic cholangitis, 2 of which also showed mild fibrosis of the periportal areas consistent with the concept of "cholangiolitic cirrhosis"[34]. The 4th patient showed a diffuse infiltration of inflammatory cells as well as portal area infiltration. In addition to the 4 patients showing chronic cholangitis

in this group, 2 patients in Group IV (hepatomegaly of undetermined etiology) also showed histopathological evidence of chronic cholangitis.

B. Correlation of Histopathological and Biochemical Observations. The biochemical findings are in general agreement with those reported in the literature[15,29,31]. Of the 4 patients exhibiting inflammatory changes on biopsy, 1 (No. 40) was unsupported by abnormal liver function tests. The remaining 3 patients demonstrated abnormal thymol turbidity tests, and 2 of the 3 showed mild retention of bromsulfalein. Both patients in Group IV (hepatomegaly) who showed histopathological evidence of chronic cholangitis also showed abnormal thymol turbidity tests.

Of the 6 patients demonstrating no abnormality of the biopsy specimen, 3 showed abnormal thymol turbidity tests. One patient in particular was of interest (No. 38) in that he gave a history of recurrent jaundice, exhibited an icterus index of 16 during his hospitalization, and showed abnormalities of the bromsulfalein and thymol turbidity tests, despite repeated normal biopsies. This finding of the residual disturbance of liver function in the absence of equivalent histopathological evidence of residual hepatocellular damage has been postulated by Watson and Hoffbauer[34] to be due to increased permeability of the cholangioles as a residual effect of the infection upon the intrahepatic biliary system.

Finally, 3 of the 6 patients showing a normal biopsy revealed no disturbance of liver function studies to support the diagnosis. These patients' symptoms which included a vague symptom complex or anorexia, easy fatigability, mild digestive disturbances and weight loss are best explained on the basis of "post hepatitis syndrome"[7], wherein the liver biopsy and all laboratory data are normal in the presence of post-hepatitis symptomatology.

The relationship of cholangiolitic fibrosis, as noted above in 2 patients, to portal cirrhosis is worthy of comment. Our observations are in accord with those of Watson and Hoffbauer[34], who offer convincing evidence for the transition of hepatitis to cholangiolitic fibrosis. However, there seems to be inadequate proof of the latter progressing to a state of frank portal cirrhosis. Rather, the periportal fibrosis following severe and, or, prolonged hepatitis appears to be a self limited and reparative process which does not progress further. Although Krarup and Roholm seemingly have been able to follow the transition of acute infectious hepatitis to cirrhosis, the poor nutritional status of the patients studied by these investigators may have been more important etiologically than the acute antecedent hepatitis. Furthermore, the fallacy of drawing conclusions as to an etiological relationship on the basis of a history of jaundice has been impressed upon us. We have had occasion to study at least 2 patients with completely negative past medical histories, but who were jaundiced on admission and had had an onset of their illnesses suggesting infectious hepatitis only 5 days previously. Liver biopsies taken 7 days after the first symptoms appeared showed histological evidence of well advanced cirrhosis. The occasional difficulties of reaching an accurate diagnosis without histological evidence as to acute hepatitis versus an acute exacerbation of cirrhosis seems obvious. By the same token, there is a pitfall in concluding that a patient with a past history of jaundice and other suggestive symptoms has developed cirrhosis on the basis of infectious hepatitis.

Group IV. **Hepatomegaly—Etiology Undetermined.** This group comprised 12 cases of hepatomegaly of clinically

undetermined etiology. The primary objective was to determine the significance of an isolated finding of hepatomegaly in the absence of other symptoms and signs referable to the liver. A liver edge palpable 4 cm. or more below the right costal margin on full inspiration was arbitrarily regarded as abnormally accessible to examination; and, in the absence of factors (such as pulmonary emphysema) tending to depress the organ lower into the abdominal cavity, was presumed to be enlarged. That such accessibility is not necessarily indicative of pathological changes in the liver was demonstrated by normal histological specimens and biochemical studies in 7 of the 12 patients. In 5 patients abnormal histopathological findings were obtained. In one (No. 49) a diagnosis of well advanced portal cirrhosis, and in another (No. 44) of early portal cirrhosis (hypertrophic fatty stage) was established. In 2 (Nos. 48 and 52) the existence of a chronic cholangitis was ascertained. The 5th patient was very obese and the liver biopsy showed fatty infiltration (No. 55). The thymol turbidity test was abnormal in both cases of cholangitis; whereas, the other function studies were normal. In the patients with cirrhosis, the bromsulfalein excretion was delayed in both and the thymol turbidity abnormal in only one. The obese patient showed mildly abnormal bromsulfalein retention and thymol turbidity tests. The glucose tolerance test was markedly abnormal which may be due to fatty infiltration of the liver as suggested by Newburgh and Conn[30]. The observation made upon our patient would tend to support this postulate, since the tolerance test returned to normal and a repeat liver biopsy was normal following weight reduction. In all instances of the patients in this group, therapy could be more intelligently directed after the biopsy examination.

GROUP V. **Hepatomegaly Due to Congestive Heart Failure**. These 5 patients presented moderate to marked hepatomegaly in association with congestive heart failure of long standing. In 3 cases failure had been present intermittently for more than 2 years, with from 3 to 8 episodes of decompensation, alternating with periods of restoration of myocardial function. The patients were all in a state of remission at the time of biopsy, although hepatomegaly persisted. The desire to know whether these livers demonstrated any of the histological features comprising so-called "cardiac cirrhosis" prompted their inclusion in the series.

Of the 5 patients biopsied, none showed sufficient histopathological criteria for making a diagnosis of cardiac cirrhosis. Three patients exhibited, except for passive congestion, normal biopsies; whereas, 2 showed, in addition to passive congestion, a mild fatty metamorphosis with no evidence of central or portal fibrosis.

Four of the 5 patients, although failing to demonstrate cardiac cirrhosis, exhibited significant retention of bromsulfalein dye, and one of them also showed an increased thymol turbidity test and a serum bilirubin slightly above the upper limit of normal. The disturbance of hepatic function roughly paralleled the degree of congestive failure, and regressed toward normal with improvement in compensation. Similar findings, particularly with respect to the bromsulfalein test, have been previously reported[22,23]. Abnormal glucose tolerance curves were obtained in 2 of 4 cases upon whom the tests were performed.

The existence and nature of cardiac cirrhosis have been a much debated subject since the first investigations into the problem[4]. All investigators are rather consistent in their opinions as to the rarity of the entity, the necessity pathogenetically for prolonged

continuous or multiple episodes of cardiac decompensation and the lack of reliable criteria for making a diagnosis of the condition[5]. The possibility of an underlying portal cirrhosis with superimposed cardiac failure must always be borne in mind, as exemplified by 2 patients in Group I who developed congestive heart failure as a complication of cirrhosis. One of these (No. 22) had been diagnosed as having cirrhosis 10 years previously. Two years before admission he first developed cardiac failure accompanied by jaundice which cleared as his cardiac status improved. The degree of abnormality of liver function studies paralleled the cardiac status. Although the second patient (No. 23) did not have a previous history of liver disease, jaundice, which was present on admission, disappeared as the cardiac failure improved. Apparently these already damaged livers were unable to withstand the added insult of cardiac failure and the resulting venous congestion. These observations suggest how a case of portal cirrhosis with superimposed cardiac failure might be misinterpreted both by the clinician and the pathologist as primary "cardiac cirrhosis".

Group VI. **Sarcoidosis.** The diagnosis prior to the liver biopsies on the patients in this group was made on the basis of clinical and roentgenological manifestations in all instances. All had had recent mild exacerbation of symptoms. In only 3 patients had histopathological confirmation of the clinical diagnosis been obtained by a lymph node biopsy, although this procedure was completed on all 6 patients. In 5 of the 6 liver biopsies, lesions of sarcoid were found. Therefore, in the absence of positive histopathological findings on peripheral node examination, the liver biopsy should be remembered when sarcoidosis is suspected clinically. It is most likely to give positive results after a period of acute exacerbation of symptoms. The abnormal liver function studies seen in 4 patients suggest that the elevated globulin, so frequently noted in this disease, may be on the basis of parenchymatous hepatic pathology. In addition these observations again emphasize the generalized nature of sarcoidosis.

Group VII. **Controls.** This group comprised 16 normal subjects who served as controls. All save one (No. 74) exhibited a normal biopsy; the exception showed minimal cholangiolitis. This latter patient gave no history of jaundice or infectious hepatitis in the past. The finding in this case raises the question of the pathological significance in the histopathological interpretation of biopsy specimens showing minimal changes consistent with cholangiolitis. Liver function tests done on selected cases from the control group were all within the normal range, including the one control subject upon whom a mild cholangiolitis was observed.

Applications of Liver Biopsy. Needle biopsy of the liver has found its greatest usefulness as an adjunct in the diagnosis of primary and secondary diffuse parenchymatous liver disease. It has been particularly useful in elucidating unexplained hepatomegaly. Some investigators[5,26] have also found it useful in the diagnosis of neoplastic diseases of the liver. Its value here depends largely on the view of the interpreter. It may also be used in the differentiation of medical and surgical jaundice. Of equal importance in parenchymatous liver disease is the value of liver biopsy as a guide to therapy. Serial biopsies on a sufficient number of patients with cirrhosis will not only serve to establish a more ideal base line for matching patients before treatment against histopathologically similar controls, but also will provide objective histopathological criteria for

evaluating the effects of various diets and other therapeutic adjuncts (vitamins, amino acids, lipotropes, liver extracts).

Summary and Conclusions. 1. The results of liver biopsies performed upon a heterogeneous group of patients has been evaluated. This included 16 control subjects who exhibited no evidences of hepatic disease. An attempt has been made to correlate the histopathological findings with the clinical and biochemical observations.

2. Approximately 70% of patients clinically diagnosed as having portal cirrhosis showed histopathological evidence of unequivocal portal cirrhosis and 30% showed fatty metamorphosis only. Hepatomegaly instead of a small atrophic liver was usually observed. Of the liver function tests employed, the bromsulfalein test showed the most consistent correlation with the histopathological findings. There seemed to be a rough correlation between the extent of hepatic cellular damage and the abnormalities displayed by these function tests. No correlation existed between the degree of fibrosis and fatty metamorphosis and the degree of altered glucose tolerance despite the high percentage of cases showing decreased tolerance (90%).

3. In acute hepatitis, no histopathological or biochemical characteristics were noted despite differences in etiology.

4. In a group of 10 patients clinically diagnosed as having chronic, recurrent hepatitis, 4 showed substantiating histopathological findings, one of whom showed no abnormal liver function studies. Half of the patients with normal biopsies revealed disturbances of liver function studies, particularly noted in the thymol turbidity test. This test appears to be most sensitive and the last to revert to normal during convalescence. Periportal fibrosis as a sequel to chronic recurrent hepatitis

TABLE 3.—OBSERVATIONS ON CONTROL SUBJECTS, SARCOIDOSIS AND CONGESTIVE HEPATOMEGALY

Case No.	*Histopathological Diagnosis*	*RBC (mil)*	*Hg (%)*	*Sed. Rate (mm/hr)*	*Serum Proteins (gm/100 cc)*	**BSP (% Ret.)*	***Thymol Turbidity (units)*	*Icterus Index*	*Serum Bilirubin (mg/100 cc)*	****Glucose Tolerance (decreased)*
	GROUP V. CONGESTIVE HEPATOMEGALY (Clinically Diagnosed)									
56.	Fatty metamorph. with passive congestion	—	100	—	7.4 (5.1/2.3)	12	—	6	1.0	—
57.	Normal liver with passive congestion	4.1	95	33	7.8 (5.0/2.8)	18	4	4	0.6	Mildly
58.	Fatty metamorph., mild, with passive congestion	4.4	90	55	8.2 (4.8/3.4)	25	15	8	1.5	Normal
59.	Normal liver with passive congestion	4.2	80	28	6.7 (4.4/2.3)	29	4	4	—	Mildly
60.	Normal liver with passive congestion	4.4	—	36	7.2 (—)	6	3	6	—	Flat curve
	GROUP VI. SARCOIDOSIS									
61.	Normal liver	4.3	85	24	7.5 (4.1/3.4)	21	22	12	0.6	—
62.	Sarcoidosis	—	80	—	7.2 (4.9/2.3)	4	1	4	—	Mildly
63.	Sarcoidosis	4.6	90	18	7.4 (4.4/3.0)	16	9	6	—	—
64.	Sarcoidosis	4.5	90	—	8.5 (3.5/5.0)	13	9	14	—	Normal
65.	Sarcoidosis	3.6	80	21	7.3 (3.3/4.0)	2	3.4	—	0.7	Mildly
66.	Sarcoidosis	4.8	95	22	7.5 (3.5/4.0)	26	8	—	—	—
	GROUP VII. CONTROL GROUP									
67.	Normal liver	—	100	10	7.3 (—)	4	6.6	6	—	—
68.	Normal liver	—	100	7	7.5 (4.5/3.0)	2	4.4	6	—	—
69.	Normal liver	—	90	—	—	6	—	6	—	Normal
70.	Normal liver	—	100	—	—	—	—	—	—	—
71.	Normal liver	—	100	—	7.8 (4.8/3.0)	—	4.2	6	—	Normal
72.	Normal liver	—	100	—	—	—	4.2	6	—	—
73.	Normal liver	—	—	1	6.8 (4.8/1.8)	2	6.0	3	—	—
74.	Cholangiolitis, mild	5.8	100	33	8.2 (5.2/3.0)	1	3	3	0.2	Normal
75.	Normal liver	4.9	100	2	7.0 (4.0/3.0)	4	6.0	3	0.2	—
76.	Normal liver	—	100	8	7.5 (5.2/2.3)	1	4	4	—	—
77.	Normal liver	—	90	23	8.2 (5.1/3.1)	4	1.5	4	—	Normal
78.	Normal liver	—	90	5	7.7 (5.2/2.5)	1	2	4	0.9	Normal
79.	Normal liver	4.0	80	21	7.0 (4.9/2.1)	2	4.6	4	—	—
80.	Normal liver	—	100	15	8.0 (5.6/2.4)	1	3.5	4	0.2	—
81.	Normal liver	—	90	15	7.5 (5.2/2.3)	0	—	4	—	Normal
82.	Normal liver	4.9	80	18	7.0 (5.0/2.0)	2	6.5	4	—	Normal

*, **, *** For footnotes, see Table 1

was observed. However there was insufficient evidence to lead to the conclusion that this pathological state progresses to advanced portal cirrhosis. A history of jaundice in the patient with cirrhosis does not warrant the assumption that infectious hepatitis has been the forerunner of cirrhosis.

5. A liver palpable 4 cm. or more below the costal margin is not necessarily indicative of hepatic disease.

6. Congestive hepatomegaly may show the same types of disturbance in liver function that are seen in portal cirrhosis; the degree of abnormality usually paralleling the cardiac status.

7. Sarcoidosis frequently exhibits typical hepatic lesions, particularly following any recrudescence of symptoms. The liver biopsy may be of considerable aid in reaching a diagnosis in the absence of peripheral lymph node involvement.

8. In a group of 16 control subjects, 15 had normal liver function studies and normal biopsies. The 16th showed evidence of minimal cholangiolitis in the absence of a past history of jaundice or biliary disease, and in the presence of normal liver function studies. This finding raises the question of the pathological significance of minimal changes suggesting cholangiolitis in the biopsy specimen.

9. The liver biopsy is of greatest value in the diagnosis of parenchymatous liver disease, and the evaluation of therapy.

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COMPARATIVE STUDIES OF "LIVER TESTS" AND ELECTROPHORETIC ANALYSES OF SERUM PROTEINS IN PORTAL AND BILIARY CIRRHOSIS

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The comparative study of hepatic function in portal and biliary cirrhosis is of theoretical as well as practical importance. Portal cirrhosis is primarily a parenchymatous liver disease; in biliary cirrhosis the involvement of the parenchyma is secondary to the obstruction and infection of the biliary tract. In the present report these 2 conditions resulting in fibrosis of the liver are compared with respect to "liver tests" most widely used at present and electrophoretic analysis of the serum proteins.

Material and Methods. The case material consists of 65 patients with portal cirrhosis and 48 with biliary cirrhosis. Histologic confirmation of the clinical diagnosis by autopsy or laparotomy or punch biopsy was obtained in all but 2 cases of biliary cirrhosis. Patients with cholangitic and cholangiolitic biliary cirrhosis considered separately before[23] are now grouped together.

For the purpose of analysis the patients with both diseases have been further subdivided according to the degree of jaundice—the 1st group without jaundice, the 2nd with moderate jaundice (the total bilirubin values were below 5 mg. per 100 cc.), and the 3rd with marked jaundice (the total bilirubin values being above 5 mg.).

The tests selected were the most widely used in differential diagnosis of liver disease, so-called "tests of hepatic function". These tests were performed by the usual methods as previously described[25]. Electrophoretic analyses were done with standard apparatus and technique[18] using sodium diethylbarbiturate (veronal) buffer of pH 8.6 and ionic strength 0.1.

Results. *Serum Bilirubin.* Jaundice was present in approximately half, or 34, of the 66 cases of portal cirrhosis and in three quarters, or 36, of the 48 cases of biliary cirrhosis.

The most intense jaundice of the series occurred in a fatal case of portal cirrhosis with direct reacting bilirubin of 39.8 and total bilirubin of 56.2 mg. per 100 cc. and absent urinary and fecal urobilinogen. The highest serum bilirubin in biliary cirrhosis occurred in a fatal case with direct reacting bilirubin of 37 and total bilirubin of 41 mg. per 100 cc.

Alkaline Phosphatase. The cases of biliary cirrhosis showed considerably higher phosphatase values than the cases of portal cirrhosis in both jaundiced and non-jaundiced groups.

In the group without jaundice 9 of 12 cases of biliary cirrhosis had phosphatase values above 10 Bodansky units, while values over 10 units were seen in only 2 of 28 cases of portal cirrhosis. Half of the cases with portal cirrhosis had values below 4.4 units, while only one case of biliary cirrhosis (asymptomatic for 2 years) had less than 4.4 units.

In the jaundiced cases of portal cirrhosis slight elevation of alkaline phos-

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phatase was frequent, but values above 10 units were rare. In contrast, the patients with biliary cirrhosis had values over 10 units in 12 of 13 moderately jaundiced cases and in 17 of 18 markedly jaundiced cases. Moreover, values above 50 units were seen only in biliary cirrhosis.

Total Serum Cholesterol. Contrast was evident between jaundiced cases of the 2 diseases. The portal cirrhosis cases showed normal or low values, while the biliary cirrhosis cases often had elevated cholesterol values (seen in 12 of the 15 markedly jaundiced cases) and these sometimes reached extremely high levels, above 1000 mg. per 100 cc.

Cholesterol Esters. Lowered cholesterol esters were most common in the jaundiced cases of both diseases, especially the markedly jaundiced cases. Among non-jaundiced cases, lowered esterified cholesterol values were more frequent in biliary than in portal cirrhosis.

Prothrombin Level. Lowered prothrombin levels below 85% following intravenous Vitamin K administration were rare in all groups of patients with biliary cirrhosis, occurring in only 4 out of 40 cases. In contrast, levels below 85% occurred in 32 of 51 cases of portal cirrhosis, 85% of the moderately jaundiced patients and 92% of the markedly jaundiced patients with portal cirrhosis exhibiting hypoprothrombinemia.

Hippuric Acid Excretion. Diminution of hippuric acid excretion below 0.7 gm. was much more prevalent in portal cirrhosis than in biliary cirrhosis in both jaundiced and non-jaundiced groups. Thus values below 0.7 gm. occurred in 20 of 27 cases of portal cirrhosis but in only 8 of 30 cases of biliary cirrhosis.

Urinary and Fecal Urobilinogen. Abnormal urinary urobilinogen excretion occurred in both portal and biliary cirrhosis. The test was abnormal in all cases of portal cirrhosis with marked jaundice. Considerable variation in urinary urobilinogen was found in biliary cirrhosis and elevated values were not uncommon. Normal values were observed in 7 of 11 cases with moderate jaundice and in 4 of 8 cases with marked jaundice.

It was unusual to find elevated fecal urobilinogen in both diseases. Absence of fecal and urinary urobilinogen occurred in 8 of 13 markedly jaundiced cases of portal cirrhosis and in only 1 case of biliary cirrhosis.

Total Plasma Proteins. Hypoproteinemia was more frequent in the jaundiced cases of both types of cirrhosis, but no significant difference could be found between the two.

Plasma Albumin. In both types of cirrhosis, hypoalbuminemia was more prevalent in jaundiced cases, but this relation was much more striking in portal cirrhosis, where albumin values below 4 gm. per 100 cc. occurred in only 32% of the non-jaundiced cases, but in all of the jaundiced cases. Albumin values below 3 gm. per 100 cc. occurred in only 3 of 36 jaundiced cases of biliary cirrhosis, but were present in 19 of 30 jaundiced cases of portal cirrhosis (11 of the 15 markedly jaundiced cases).

Plasma Globulin. Increase in globulin values above 3 gm. per 100 cc. occurred in both portal and biliary cirrhosis but much less frequently in the non-jaundiced cases.

Cephalin-Cholesterol Flocculation. Normal values (2+ or less) occurred in 32 of 44 cases of biliary cirrhosis and the incidence bore little relation to presence or absence of jaundice. In contrast, patients with portal cirrhosis exhibited a markedly higher incidence of abnormal tests in the presence of jaundice, 23 of the 29 jaundiced cases having 3+ or 4+, while only 8 of 31

TABLE 1.—COMPARATIVE VALUES OF "LIVER TESTS" IN PORTAL AND BILIARY CIRRHOSIS

		Cirrhosis					
		No Jaundice		Mod. Jaundice <5.0 mg. Bilirubin		Marked Jaundice >5.0 mg. Bilirubin	
"Liver Tests"	*Normals*	*Portal*	*Biliary*	*Portal*	*Biliary*	*Portal*	*Biliary*
Alkaline Phosphatase (Bodansky units)							
<4.4	20	14	1	2	–	4	–
4.4–7.0	—	11	1	4	1	3	1
7–10	—	1	1	4	–	1	–
10–20	—	2	2	1	3	4	3
20–50	—	–	6	–	5	–	12
>50		–	1	–	4	–	2
Total		28	12	11	13	12	18
Total Cholesterol (mg. per 100 cc.)							
>500	—	–	–	–	2	–	5
500–400	—	1	2	–	3	–	3
400–300	—	5	2	–	4	–	4
300–140	20	19	5	14	4	9	3
<140	—	3	–	2	1	3	–
Total	20	28	9	16	14	12	15
% Cholesterol esterified							
80–60	19	23	6	12	10	1	4
60–40	1	1	3	2	3	5	4
<40	—	2	1	2	3	8	7
Total	20	26	10	16	16	14	15
Prothrombin Level (%)							
100–85	19	16	10	2	10	1	14
85–70	1	9	–	8	2	3	2
70–50	—	–	–	3	–	8	–
<50	—	–	–	–	–	1	–
Total	20	25	10	13	12	13	16
Hippuric Acid (gm.)							
>0.7	20	6	7	1	9	–	6
0.5–0.7	—	5	–	3	1	2	4
0.3–.05	—	2	1	1	1	1	–
<0.3	—	1	–	2	–	3	1
Total	20	14	8	7	11	6	11
Urinary Urobilinogen (mg. per diem)							
<3.0	20	12	7	2	7	(8)	4 (1)
3.0–10	—	4	–	1	2	1	1
10.0–20	—	1	1	1	1	–	2
>20	—	–	–	7	1	4	1
Total	20	17	8	11	11	13	8
Fecal Urobilinogen (mg. per diem)							
>300	—	2	2	1	1	1	–
300–20	20	13	4	10	6	3	3
20–5.0	—	2	–	–	3	–	4
<5.0	—	–	–	–	1	(8)	(1)
Total	20	17	6	11	11	12	8
Total Plasma Proteins (gm. per 100 cc.)							
>7.0	8	17	3	8	9	1	3
7.0–6.0	12	10	7	3	5	8	6
6.0–5.0	—	7	1	5	3	4	9
<5.0	—	–	–	–	–	3	–
Total	20	34	11	16	17	16	18
Plasma Albumin (gm. per 100 cc.)							
>4.0	20	23	7	–	7	–	4
4.0–3.0	—	7	4	7	10	4	12
3.0–2.0	—	4	–	8	1	7	2
<2.0	—	–	–	–	–	4	–
Total	20	34	11	15	18	15	18
Plasma Globulin (gm. per 100 cc.)							
>4.0	—	2	–	6	5	4	2
4.0–3.0	—	6	3	8	6	4	9
3.0–2.5	4	25	5	2	5	7	5
<2.5	16	1	3	–	2	–	2
Total	20	34	11	16	18	15	18
Cephalin-Cholesterol Flocculation							
Negative	13	12	6	–	6	–	6
+	6	6	2	2	4	1	3
++	1	5	1	1	1	2	3
+++	—	7	2	5	3	8	3
++++	—	1	1	6	2	4	1
Total	20	31	12	14	16	15	16
Thymol Turbidity (units)							
0–4	14	11	6	–	4	–	4
4–7	6	8	3	2	5	3	3
7–10	—	4	1	1	3	2	4
10–15	—	1	2	5	1	4	1
>15	—	–	–	6	5	5	3
Total	20	24	12	14	18	14	15

( ) Indicates absence of both fecal and urinary urobilinogen.

non-jaundiced cases had values of 3+ or 4+.

Thymol Turbidity Test. The findings were similar to those of the cephalin-cholesterol flocculation test. Normal values occurred in 25 of 45 cases of biliary cirrhosis and the incidence showed little relation to the presence or absence of jaundice. In contrast, patients with portal cirrhosis showed a markedly higher incidence of abnormal tests in the presence of jaundice, 23 of 28 jaundiced cases having values over 7 units while only 5 of 24 non-jaundiced cases had values over 7 units.

Thymol turbidities above 15 units occurred only in jaundiced cases of both types of cirrhosis.

Electrophoretic Studies of the Serum Proteins. The findings in 10 cases of biliary cirrhosis and 12 cases of portal cirrhosis are listed in Table 2, in comparison with the mean values from 10 volunteer subjects with normal tests of hepatic function.

Fig. 1 illustrates electrophoretic patterns of the serum proteins in a normal control and in cases of the 2 types of cirrhosis of varying severity.

Patient W. H. had become asyptomatic after his common duct was successfully repaired following 2 earlier

TABLE 2.—THE FINDINGS IN 10 CASES OF BILIARY CIRRHOSIS AND 12 CASES OF PORTAL CIRRHOSIS

	Electrophoretic Data											*Howe Sodium Sulfate Gm. per 100 cc.*			
	%					*Gm. per 100 cc.*									
	Alb.	α_1	α_2	β	γ	*Alb.*	α_1	α_2	β	γ	*A/G*	*A/G*	*Alb.*	*Glob.*	*Total*
BILIARY CIRRHOSIS															
Without Jaundice															
W. H.	54.6	5.0	9.0	17.7	13.7	3.78	0.35	0.62	1.22	0.95	1.20	2.04	4.64	2.28	6.92
M. F.	44.8	5.4	10.2	16.3	23.3	3.40	0.41	0.78	1.24	1.77	0.81	1.33	4.34	3.26	7.60
With Jaundice															
T. O.	42.1	6.6	13.3	27.9	10.1	2.69	0.42	0.85	1.79	0.65	0.73	1.91	4.20	2.20	6.40
M. G.	47.9	4.1	9.2	20.3	18.5	3.44	0.29	0.66	1.46	1.33	0.92	1.37	4.15	3.03	7.18
C. M.	40.8	7.2	16.1	15.7	20.2	2.49	0.44	0.98	0.96	1.23	0.69	1.44	3.60	2.50	6.10
F. F.	37.8	8.8	16.3	21.0	16.1	2.47	0.57	1.06	1.37	1.05	0.61	1.19	3.54	2.98	6.52
K. V.	36.9	6.9	12.1	23.7	20.4	2.03	0.38	0.67	1.30	1.12	0.59	1.08	2.86	2.64	5.50
M. E.	39.0	6.6	9.4	18.8	26.2	3.12	0.53	0.75	1.50	2.10	0.64	0.98	3.95	4.05	8.00
L. S.	29.6	5.3	9.3	25.6	30.2	2.53	0.45	0.79	2.19	2.58	0.42	0.72	3.58	4.96	8.54
L. H.	32.4	6.0	10.9	32.7	18.0	2.92	0.54	0.99	2.95	1.63	0.48	0.80	4.00	5.03	9.03
PORTAL CIRRHOSIS															
a. Asymptomatic Without Jaundice															
J. C.	55.1	5.9	14.3	13.7	11.0	3.61	0.39	0.94	0.90	0.72	1.23	1.07	3.41	3.15	6.56
M. M.	52.2	4.0	10.4	18.6	14.8	4.14	0.32	0.83	1.47	1.17	1.09	1.61	4.89	3.04	7.93
D. B.	55.2	4.5	10.3	17.8	12.2	3.99	0.33	0.74	1.29	0.88	1.23	1.91	4.75	2.48	7.23
b. With Symptoms but Without Jaundice															
P. F.*	36.2	7.1	7.5	17.4	31.8	1.88	0.37	0.39	0.91	1.66	0.57	0.94	2.53	2.68	5.21
I. B.	36.9	8.0	9.1	16.9	29.1	2.70	0.58	0.67	1.24	2.13	0.58	0.79	3.23	4.09	7.32
M. D.	50.0	5.2	6.6	15.9	22.3	3.15	0.33	0.42	1.00	1.40	1.00	1.74	4.00	2.30	6.30
With Jaundice															
J. K.*	33.3	4.1	7.4	26.9	28.3	1.87	0.23	0.41	1.51	1.59	0.50	0.58	2.05	3.56	5.61
J. B.*	28.1	2.2	4.3	32.6	32.8	1.82	0.14	0.28	2.10	2.12	0.39	0.44	1.96	4.50	6.46
M. S.*	31.0	5.0	8.0	17.0	39.0	2.01	0.32	0.52	1.10	2.53	0.45	0.65	2.56	3.92	6.48
R. D.*	38.1	4.1	6.4	12.6	38.8	2.56	0.28	0.43	0.85	2.61	0.62	0.80	2.99	3.74	6.73
G. K.	37.7	6.0	10.4	23.7	22.2	2.89	0.46	0.80	1.82	1.71	0.60	0.84	3.50	4.18	7.68
B. K.	48.1	3.8	15.5	8.3	24.3	3.58	0.28	1.15	0.62	1.81	0.93	1.46	4.42	3.02	7.44
AVERAGE VALUES															
Biliary Cirrhosis without Jaundice	49.7	5.2	9.6	17.0	18.5	3.59	0.38	0.70	1.23	1.36	1.05	1.68	4.49	2.77	7.26
Portal Cirrhosis without Jaundice															
Asymptomatic	54.2	4.8	11.7	16.7	12.7	3.91	0.35	0.84	1.22	0.92	1.18	1.53	4.35	2.89	7.24
With Symptoms	41.0	6.8	7.7	16.7	27.7	2.58	0.43	0.49	1.05	1.73	0.77	1.16	3.25	3.02	6.28
Biliary Cirrhosis with Jaundice	38.3	6.4	12.1	23.2	20.0	2.71	0.45	0.84	1.69	1.46	0.64	1.19	3.74	3.42	7.16
Portal Cirrhosis with Jaundice	36.1	4.2	8.7	20.2	30.9	2.46	0.29	0.60	1.33	2.06	0.58	0.79	2.91	3.82	6.73
Normals	60.3	4.0	9.7	12.8	13.2	4.23	0.28	0.68	0.89	0.93	1.52	2.31	4.89	2.12	7.01

* Presence of ascites

unsuccessful operative attempts. He has remained well on full activity for over a year with normal serum bilirubin and tests of hepatic function. The electrophoretic pattern reveals relatively minor deviations from normal.

Patient D. B. was a case of "latent" portal cirrhosis with no symptoms of liver disease. Because of the incidental physical finding of an enlarged liver, a needle biopsy was done which revealed marked fibrosis and fatty infiltration. The serum bilirubin was normal, as were the liver tests with the exception of bromsulfalein retention of 38%. The electrophoretic pattern in this asymptomatic case likewise is nearly normal.

On the other hand, in patients with more advanced liver disease and clinical evidence of hepatic insufficiency, the serum proteins manifested striking abnormalities on electrophoretic analysis. Diminution of the albumin fraction and elevation of the globulins, notably the gamma-globulin fraction, almost always occurred. In such relatively advanced cases, moreover, differences between portal and biliary cirrhosis were readily apparent.

The electrophoretic patterns in Fig. 1 from cases of portal cirrhosis with hepatic insufficiency, namely, patients P. F., R. D., and J. B., all show marked diminution of the albumin fractions and elevation of the gamma-globulins. Case P. F., with massive edema and ascites, had the most abnormal pattern of the non-jaundiced group. Cases R. D. and J. B., both with jaundice, edema, and ascites, had markedly abnormal patterns, though differing in that R. D. had a normal beta-globulin while J. B. had a markedly elevated double-peaked beta-globulin, the highest observed among the cases of portal cirrhosis. The data of Table 2 show gamma globulin elevations in all cases of portal cirrhosis except the asymptomatic group. Increases in other globulin fractions including beta-globulin occurred with less regularity.

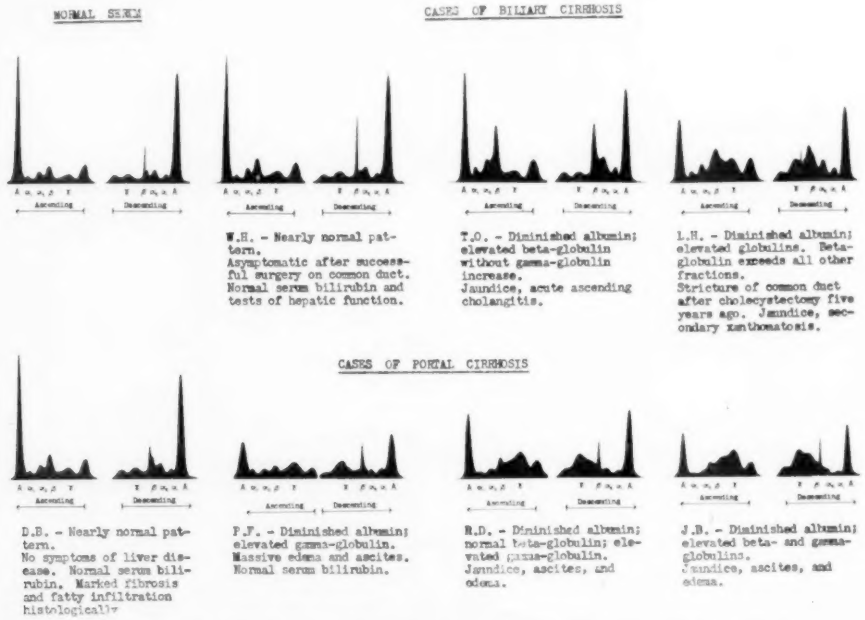
NORMAL SERUM
CASES OF BILIARY CIRRHOSIS
W.H. - Nearly normal pattern.
Asymptomatic after successful surgery on common duct.
Normal serum bilirubin and tests of hepatic function.
T.O. - Diminished albumin; elevated beta-globulin without gamma-globulin increase.
Jaundice, acute ascending cholangitis.
L.H. - Diminished albumin; elevated globulins. Beta-globulin exceeds all other fractions.
Stricture of common duct after cholecystectomy five years ago. Jaundice, secondary xanthomatosis.
CASES OF PORTAL CIRRHOSIS
D.B. - Nearly normal pattern.
No symptoms of liver disease. Normal serum bilirubin. Marked fibrosis and fatty infiltration histologically.
P.F. - Diminished albumin; elevated gamma-globulin.
Massive edema and ascites.
Normal serum bilirubin.
R.D. - Diminished albumin; normal beta-globulin; elevated gamma-globulin.
Jaundice, ascites, and edema.
J.B. - Diminished albumin; elevated beta- and gamma-globulins.
Jaundice, ascites, and edema.

FIG. 1.—Electrophoretic Patterns of the Serum Proteins in Portal and Biliary Cirrhosis.

The patterns in Fig. 1 from the cases of biliary cirrhosis, Patients T. O. and L. H., reveal conspicuously steep beta-globulin peaks which distinguish them from the portal cirrhosis patterns even when the latter do show marked beta-globulin elevation as in the case of J. B. The pattern of T. O. revealed some diminution of albumin, and a very steep beta-globulin peak but normal gamma-globulin. The pattern of L. H. revealed diminished albumin, elevated gamma-globulin, and a steep beta-globulin peak, this fraction exceeding all others. The possible significance of the elevated beta-globulin in biliary cirrhosis is discussed below.

Discussion. Previous work has indicated that in portal cirrhosis alterations in hepatic function[23] and symptoms of liver failure[24] are not related to the degree of fibrosis but depend on the degree of parenchymal damage[26]. Moreover, severe hepatic failure was found most often in severely jaundiced patients[24]. In the present series the tests considered to express parenchymal function, namely, prothrombin level, urinary urobilinogen, hippuric acid excretion, and also cephalin flocculation and thymol turbidity, showed abnormalities in general though by no means uniform correlation with the degree of jaundice. In biliary cirrhosis, on the contrary, there was no such consistency but instead a marked irregularity of impairment of the tests of parenchymal function and little parallelism between these tests and degree of jaundice. Many severely jaundiced cases had normal or slightly abnormal hippuric acid excretion, urinary urobilinogen, cephalin flocculation, or thymol turbidity. The prothrombin levels were within the normal range in almost all of the cases of biliary cirrhosis. These differences in tests expressing parenchymal function are quite similar to previous comparative studies between obstructive and parenchymatous liver disease[4,5,7,11,13,21,22,27,33].

Alkaline phosphatase values were considerably higher in biliary cirrhosis than in portal cirrhosis, some of the jaundiced cases of biliary cirrhosis having values above 50 units. The alkaline phosphatase elevation illustrates the primacy of the obstructive over the parenchymatous pathology in biliary cirrhosis. This distinction between the 2 diseases was not always clear cut, since overlapping of values occurred, particularly in jaundiced cases. These observations are similar to the findings of others who have compared obstructive and parenchymatous liver disease as reviewed by Gutman *et al.*[12]

The serum cholesterol levels were elevated in most of the jaundiced cases of biliary cirrhosis while normal or low levels were seen in portal cirrhosis. With progression of jaundice in portal cirrhosis the serum cholesterol tended to fall. These observations are in agreement with previous studies[8,9]. Epstein[8] found hypercholesterolemia is usually encountered in obstructive jaundice and roughly parallels the degree of obstruction except when associated cachexia or superimposed infections of the biliary tract are present which lower the serum cholesterol[1,8,30]. In degenerative diseases of the liver the more severe the damage the greater is the tendency to hypocholesterolemia[8]. In the present study it is shown that in both portal and biliary cirrhosis there was diminution of esterified cholesterol. In portal cirrhosis this drop parallels the severity of the hepatic parenchymal damage. In biliary cirrhosis the lowering of the esters and damage of the liver parenchyma is due to the associated obstructive and infective disease of the biliary tract. Total lipid determinations by Kunkel, Ahrens, and Eisenmenger[15] revealed abnormally high

levels in biliary cirrhosis but normal or low levels in other types of cirrhosis, the levels tending to fall parallel to the depression of the serum albumin.

The electrophoretic patterns of the serum proteins were nearly normal in cases of both types of cirrhosis with few or no clinical or laboratory evidences of active hepatic disease. In advanced cases, however, abnormal patterns were invariably observed. The alterations usually seen in diseases of the liver have previously been described by numerous investigators[10,15, 19,20,29,32]. In hepatic parenchymal disease typified by portal cirrhosis the characteristic findings are depression of the albumin fraction and elevation of the gamma-globulin fraction with less frequent elevation of the other globulins including the beta-globulin fraction.

The distinguishing feature of the electrophoretic patterns in biliary cirrhosis was the constant finding of beta-globulin elevation, sometimes reaching spectacular levels in advanced cases. These patterns exhibited steep beta-globulin peaks not seen in portal cirrhosis even when the beta-globulin was high. Kunkel and Ahrens[14], and Lever[16] have likewise reported marked beta-globulin elevations in biliary cirrhosis.

The elevated beta-globulin peak appears to be due mainly to increased beta-lipoprotein as indicated by reduction of this component by cold ether extraction[16,28] or by means of a high salt 1% phenol solution which makes possible the removal of 85 to 95% of the serum lipids[14]. In a study utilizing the latter method Kunkel and Ahrens[14] also observed a direct proportionality between electrophoretically determined beta-globulin and total serum lipid concentration. These authors[2,3] have emphasized the disproportionately high phospholipid content of these sera. The clarity of the high-lipid sera in biliary cirrhosis was attributed to the hydrophilic nature of the phospho-lipids by virtue of their water-soluble side chains. In contrast, the phospho-lipids were found to be relatively low in the lipemic (milky) sera of patients with nephrosis.

Whether the elevated serum beta-lipoprotein in biliary cirrhosis is merely a phenomenon of biliary regurgitation or whether it represents some special derangement of hepatic metabolism remains to be determined. The observations of Balfour[6] with the aid of radioactive phosphorus have suggested that the cause of elevated serum phospholipids is overproduction by the liver rather than accumulation in the blood because of biliary regurgitation.

Summary. 1. Sixty-five cases of portal cirrhosis and 48 cases of biliary cirrhosis were compared with respect to "liver tests" most widely used in the differential diagnosis of liver diseases. Electrophoretic analyses of the serum proteins of 10 cases of biliary cirrhosis and 12 cases of portal cirrhosis were also compared.

2. While a great deal of overlapping occurred in the findings in each test and in the electrophoretic studies, certain differences were noted between the 2 diseases.

3. In cases of portal cirrhosis the degree of jaundice, where present, bore a relation to the abnormalities of tests considered to express hepatic parenchymal function; in biliary cirrhosis these tests were irregularly affected.

4. Total serum cholesterol was usually normal or diminished in portal cirrhosis, but was elevated in most of the jaundiced cases of biliary cirrhosis.

5. Alkaline phosphatase values were higher in biliary than in portal cirrhosis, but there was considerable overlapping.

6. Asymptomatic cases of both diseases had nearly normal electrophoretic patterns of the serum proteins.

7. In cases with hepatic insufficiency abnormal protein patterns were observed, usually with diminution of the albumin fraction and elevation of the gamma-globulin fraction.

8. The electrophoretic patterns in biliary cirrhosis were distinguished by steep beta-globulin peaks, which were spectacularly elevated in advanced cases.

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THE MECHANISM OF THE ANAPHYLACTOID PHENOMENON

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Intravenous injections of foreign material may produce a state of shock which, because of its resemblance to anaphylaxis, has been termed the anaphylactoid phenomenon. This phenomenon was investigated extensively by Hanzlik and Karsner[2] more than a quarter of a century ago. These authors tested different agents in over 370 animals (mostly guinea pigs, a few cats, and several dogs) and characterized the phenomenon by the following anatomical findings: distention of pulmonary alveoli; pulmonary congestion and hemorrhages; thrombi and, or, emboli in pulmonary vessels; peribronchial edema; constricted arterial beading and cardiac dilation. In some animals there was also reported an associated delayed clotting of the blood. All of the above findings were not present in every animal although the characteristic symptoms of the anaphylactoid phenomenon were considered to have been demonstrated.

Our interest in the problem was stimulated when seemingly minute intravenous doses of such chemically inert materials as finely divided silica and antimony trioxide regularly and rapidly killed rabbits with symptoms suggestive of embolism. Considering the small quantity of particulate matter injected, embolism as an explanation seemed improbable. The rapidity with which the rabbits died also seemed to exclude the red cell agglutination which was demonstrated *in vitro* by Hanzlik and Karsner[4] with a number of different substances in human, cat, and guinea pig blood. Nevertheless, our findings at autopsy were typical of embolism: dilation of the right heart, pulmonary distention, and obstruction of the pulmonary vessels by acidophilic, homogeneous or finely granular material with or without polymorphonuclear leukocytes. To resolve this apparent paradox we considered the possibility that finely divided material may adsorb plasma proteins to form bulky, sticky aggregates which cause vascular obstruction. The following experiments were designed to test this theory.

Methods and Results. Clay* was the test material chosen for intravenous injection because it could be obtained in a variety of sizes of satisfactory homogeneity. The material was dispersed as a 20% suspension in water with sodium pyrophosphate as a buffer and dispersing agent. The larger sizes, down to 1 micron, were obtained by repeated settling until microscopic sizing revealed a high degree of homogeneity. The finer sizes were obtained by repeated passage through the Sharpless ultracentrifuge until uniformity was obtained, as measured by

* The clay chosen was English China clay, supplied through the kindness of Hall China Company.

electron micrographs of the dispersed dusts.

The material was suspended in phosphate solution and the pH adjusted to 7. Rabbits were then given, by intravenous injection, 0.75 ml. per kg. body weight of the suspension, containing 30 mg. of clay per ml. The results are presented in Table 1.

An inverse relationship is seen in Table 1 between the particle size of the injected material and the resulting mortality. Animals given the same dose on a weight basis exhibited 100% mortality when the particle size was 0.2 micron, while those animals receiving particles of 0.6 micron or above in size showed no significant mortality. An intermediate size (0.3 micron) produced a mortality of something less than 100%. Equal weight doses of Al_2O_3 (0.2 micron), Fe_2O_3 (0.2 micron), Carbon (0.25 and 0.08 micron), and Sb_2O_3 (0.4 micron) were also 100% lethal.

Histological examination of the lungs of animals killed by intravenous injection of the smaller size suspensions uniformly demonstrated blockage of the pulmonary vessels. Emboli of aggregated particles were clearly seen in the lung capillaries and other small vessels. These observations suggested that aggregation of the material occurred and that these aggregates blocked the pulmonary vessels, causing death. In order to test this hypothesis further, distilled water suspensions containing 30 mg. per ml. of different dusts were prepared according to the method of Brown *et al.*[1], and 0.5 ml. of each suspension was thoroughly shaken with 0.5 ml. of plasma. To each suspension 9 ml. of saline was added and the suspension again well mixed. As controls, 15 mg. of each

TABLE 1.—THE RELATION OF PARTICLE SIZE TO THE MORTALITY RATE OF RABBITS RECEIVING SUSPENSIONS OF PARTICULATE MATTER (CLAY) INTRAVENOUSLY; DOSE EQUAL TO 22.5 MG./KG.

Size of Clay microns	*Particles per mg.*	*No. of Animals*	*No. Dying*
5	16×10^9	6	0
3	77×10^9	5	0
1	200×10^9	8	1
0.6	$1{,}000 \times 10^9$	10	0
0.3	$7{,}700 \times 10^9$	8	6
0.2	$25{,}000 \times 10^9$	8	8

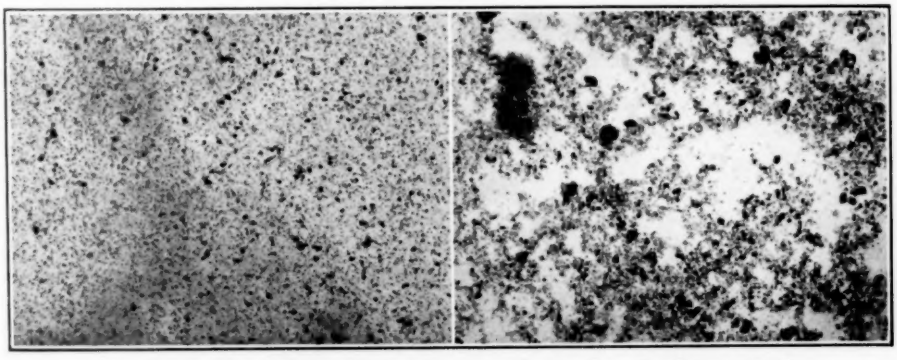

FIG. 1.—Left: Fairly uniform dispersion of particles of saline control. Right: Solid masses and loosely agglutinated particles exposed to plasma. Material is carbon of 0.2 micron diameter.

dust was suspended in 10 ml. of saline alone. All suspensions were subjected to centrifugation, the supernatant fluid discarded, and the sediment resuspended in 9.5 ml. water. One drop of each suspension was placed upon a slide and examined. The different dusts tested included clay, carbon, silica, Fe_2O_3, Al_2O_3, and Sb_2O_3. The plasma caused clumping of the dust, if of fine particle size, regardless of chemical composition. In contrast to the saline controls, such clumps could not be redispersed (Fig. 1).

Thus, the slide demonstrations paralleled the results observed by intravenous injection. The probable explanation is that the relatively large surface area of very fine particulate matter caused adsorption of protein from the plasma and thereby made the particles adhesive.

Actual proof of plasma protein adsorption was furnished by the following experiment: The several different materials of varying particle size were suspended in plasma and in saline as before. After 3 successive saline washings the centrifuged sediment was analyzed for its nitrogen content by the micro-Kjeldahl method. The difference between the nitrogen content of the dust suspended in plasma and that of the same dust (identical weight) in saline, represented the amount of nitrogen adsorbed as plasma protein. The results (Table 2) indicate that the amount of nitrogen adsorbed varies inversely with the particle size; the amount of adsorbed plasma protein ranged from 4 to 9 times the weight of the adsorbent dust.

It has also been possible to demonstrate that particle-protein aggregates, such as were observed *in vitro,* can obstruct pulmonary vessels without the participation of fibrin, platelets, or blood cells. Rabbits were anesthetized with ether, the pulmonary artery was cannulated, and the pulmonary veins opened. The lungs were perfused with saline to wash out the blood and then with human plasma which had been filtered through absorbent cotton to remove formed elements and fibrin. During the perfusion (under a constant head of pressure) there occurred changes in effective perfusion pressure which were measured with a water manometer. When plasma was substituted for saline the effective perfusion pressure rose slightly due to the greater viscosity of the plasma. A further rise in pressure to almost double the perfusion pressure obtained with plasma alone occurred promptly upon the addition of 15 mg. per 100 ml. of plasma of finely divided particulate substance (clay, Fe_2O_3), demonstrating the rapidity with which the par-

TABLE 2.—THE PROTEIN ADSORBED BY DUSTS OF VARIOUS SIZES IN PLASMA SUSPENSION

Dust	*Size (microns) (Approx. aver.)*	*Mg. N. adsorbed per 15 mg. dust**	*Mg. protein adsorbed per 15 mg. dust (N × 6.25)*
Clay	3	9.9	62
	0.6	10.4	65
	0.2	17.4	108
Carbon	0.3	11.7	73
	0.08	20.2	126
	0.01	36.6	229
Silica	0.5	9.0	56
	0.2	26.0	163
ZnO_2	0.2	19.0	119
Al_2O_3	0.5	9.6	60
Fe_2O_3	0.2	13.8	86
Sb_2O_3	0.4	9.7	61

* These values are the differences between the amounts of nitrogen found in the dust-plasma sediment and in the sediment of its saline control.

ticle-protein aggregates formed and obstructed the pulmonary vessels. Histologic sections of the perfused lungs (Fig. 2) show widespread vascular occlusions by aggregates of injected particles. This picture is similar to that obtained when the material was injected intravenously into living animals. In one test with 1-micron clay particles, no significant rise in pressure was noted.

Discussion. In terms of the present day concept of shock, it is immaterial what its precipitating cause may have been which set the basic disturbances into activity. The sequence of events presents a fairly uniform picture[5]. This concept is represented by the cycle: anoxia —> loss of semi-permeability of vascular endothelium —> loss of plasma from vessels into tissues —> reduced blood volume —> further anoxia —>. The lungs are commonly involved in shock, and endothelial damage is here characterized by pulmonary edema, congestion and alveolar hemorrhage. Because of peribronchial edema[2] and the accumulation of plasma in alveoli and bronchi, respiratory obstruction develops which results in forceful and gasping respiratory movements. These lead to the finding of pulmonary distention at autopsy. It is a common observation that intracranial hemorrhage, whether traumatic or non-traumatic in origin, furnishes some of the most outstanding examples of pulmonary distention, edema, and congestion with intra-alveolar hemorrhages.

If the above concept is accepted it becomes obvious that most of the anatomic findings of the anaphylactoid phenomenon are non-specific and may be found in shock from whatever cause. The obstruction of pulmonary capillaries with the associated dilation of the right side of the heart, however, is peculiar to, and characteristic of, the anaphylactoid phenomenon. The clinical manifestations of this phenomenon are those of air hunger, and, if the animal does not die immediately, pulmonary edema and hemorrhage develop rapidly. It is not difficult to reconcile the rapid progress of the clinical manifestations with the rapidity of pulmonary vascular obstruction,

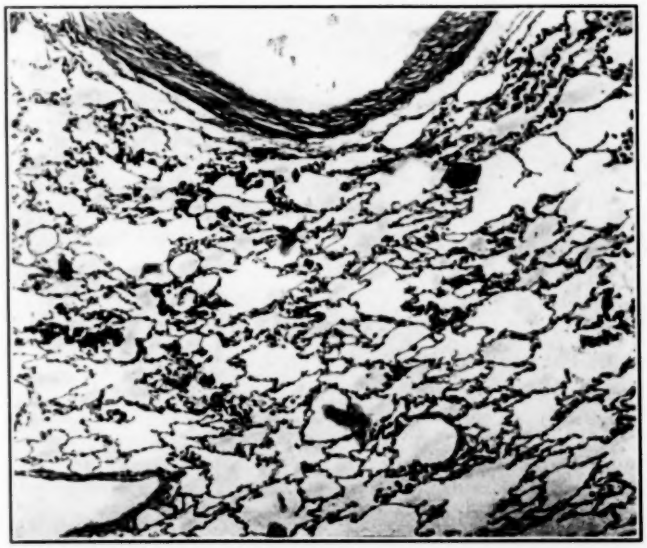

FIG. 2.—Rabbit lung perfused with blood plasma containing 15 mg. Fe_2O_3 per 100 ml. The occlusion of alveolar vessels by dense, black pigment masses is striking.

an equally rapid elevation in intravascular pressure proximal to the obstruction, and a rapid extravasation of plasma under greatly increased pressure through anoxic, damaged endothelium.

The *in vitro* demonstration of the flocculation testifies to the adhesiveness of the particle-protein aggregates. It is therefore not surprising to find in some, or many, areas entrapped platelets and, or, leukocytes associated with the emboli since these elements are known to possess adhesive surfaces. Provided that there is no impairment of blood coagulability[3], fibrin thrombi may form in the occluded vessels due to stasis, endothelial damage and perhaps also increased blood viscosity (hemoconcentration). It is very probable that the constricted arterial beading noted by Hanzlik and Karsner[3] is also a result of the reduction in blood volume.

While Novy and DeKruif[6] in 1917, and Hanzlik and Karsner[3] in 1924 observed that a smaller particle size is more lethal than a larger one on intravenous injection, our data (Table 1) represent a systematic and quantitative determination of this relationship.

Our data further indicate clearly that occlusive emboli may develop during or following the intravenous injection of finely divided particulate material without the participation of formed blood elements or fibrin. Karsner and Hanzlik[4], on the other hand, found hemagglutination a common phenomenon among agents which produce anaphylactoid symptoms and noted close correlation between hemagglutination *in vitro* and thrombus formation. They also added that this relation was by no means constant or necessary. We were unable to demonstrate hemagglutinating properties with the materials used in the present experiments.

Conclusions. 1. The only anatomic finding which is peculiar to, and characteristic of, the anaphylactoid phenomenon is pulmonary vascular occlusion (involving the smallest vessels) and the associated dilated right heart.

2. Death from diffuse pulmonary vascular occlusion may occur following the intravenous injection of small amounts of chemically inert, finely divided particulate matter.

3. The lethality of the phenomenon is a function of the particle size. In the dosage employed, particles over 0.6 micron in size did not kill, while particles 0.2 micron in size produced 100% mortality.

4. *In vitro* experiments demonstrated the formation of sticky aggregates when fine particles are suspended in blood plasma. These aggregates form as a result of adsorption of protein to the particles.

5. Chemical analysis of such aggregates washed free of plasma have demonstrated the presence of adsorbed protein. There is an inverse relationship between the particle size and the amount of protein adsorbed.

6. Perfusion of rabbit lungs with plasma free of fibrin or formed elements but containing small amounts of finely divided particulate matter resulted in pulmonary vascular occlusions identical to those seen in animals dying with symptoms typical of the anaphylactoid phenomenon.

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TREATMENT ABUSES IN ALLERGY PRACTICE*

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The widening scope of the field of allergy can be appreciated readily when one realizes that there is scarcely a tissue in the body which is not affected by allergic reactions; also that conditions as seemingly dissimilar as urticaria and periarteritis nodosa both are provoked by allergic sensitization. The clinical manifestations of allergy are so extensive that treatment of necessity is carried out much more frequently by the general practitioner, the pediatrician or the otolaryngologist than by the allergist. As a consequence, improprieties and failures in treatment follow, which in turn lead to discouragement of the patients and to misconceptions upon the part of the attending physician as to the value of such treatment. Over nearly a quarter of a century of experience with allergy patients, I have had many occasions to see the effects of these treatment improprieties which surely arise from ignorance and not from deliberate intention. It seems worth while therefore to discuss some of these treatment abuses, pointing out the reasons for their occurrence as well as the methods by which they may be prevented or controlled.

In order to understand better their origin, it is well first to review the general principles of allergy treatment. If these were more clearly understood and followed more regularly and carefully, it would minimize the treatment pitfalls.

The type of treatment that the allergic patient requires will depend upon the results of appropriate diagnostic studies. If these have revealed a specific cause or causes, the principles of treatment usually are simple—if the known excitant can be eliminated from the patient's diet (if a food) or from his environment (if an inhalant) or if contact with it can be avoided, no further treatment is needed. The dramatic effects that sometimes follow the elimination of a specific food like egg or milk or wheat, or the removal of cat or dog or horse contact from an asthmatic child, attests to the simplicity of this kind of treatment. While this is the ideal goal of all allergy treatment, it unfortunately is not easy to attain. Most allergy patients either have multiple sensitivities or are allergic to agents with which it is difficult to avoid contact or which cannot be easily eliminated (*e.g.*, plant pollen or house dust). Under those circumstances it becomes necessary to attempt to raise the tolerance of the patient by the process known as *desensitization* but perhaps more correctly as *hyposensitization*. Such desensitization is *specific* when the specific allergen to which the patient is known to be sensitive is used. It is *nonspecific* when the specific agent is not used or is unknown, but when in order to obtain similar effects, various so-called nonspecific agents are utilized. In either instance, regardless of the type of allergy treatment instituted, symptomatic relief of the patients must be provided.

These principles of allergy treatment

* Read before the Hollywood (California) Academy of Medicine, March 9, 1950.

certainly would seem simple to carry out, yet they are ignored or modified with surprising frequency. For example, specific treatment including both elimination or avoidance and specific desensitization naturally depends upon the determination of the specific offender by proper diagnostic study. If this is incorrectly done, the false information obtained will naturally result in faulty treatment. Improper diagnostic study probably is the commonest source of treatment abuse. The methods of diagnosis used in allergic diseases should be familiar to all practitioners and need not be reviewed, but their importance must be emphasized because physicians so often depend upon skin test evidence alone for specific diagnosis, instead of using it like the results of any other laboratory method in conjunction with a good history, physical examination and the results of the application of clinical trial. Misinterpretation of positive skin test reactions is a potent source of treatment error. This is because little effort is expended by the physician receiving the report to determine whether the positive skin test represents past, present or future (potential) sensitivity. Unfortunately, allergy patients are treated too often purely upon the basis of the skin tests without any attempt being made to determine their clinical significance. The general routine often is as follows: Skin tests are performed, positive reactions are obtained, then the matter seemingly is settled when the patient is given a list of the positive reactors to eliminate. Little attempt is made to determine whether the many positive reactions have clinical significance or whether they are nonclinical or nonspecific in character. Too frequently has so important a food as milk been eliminated unnecessarily from a child's diet for a long time merely upon the basis of a positive reaction to milk. Yet the child could drink it in large amounts with impunity before the tests were done. A careful history might have revealed, as it has in our experience, that such children had difficulty taking milk in infancy because of allergy to it. But as they got older, they overcame this clinical sensitization and were able to take milk again. Nevertheless, the skin, which possesses a remarkably retentive memory of past sensitization shows this imprint by a persistent positive skin reaction. This applies not only to milk but also to positive skin reactions to other foods as well which also may represent past sensitivity. How often have physicians raised their eyebrows in doubt and skepticism of the value of skin tests because of reports of positive skin reactions to foods which the patient never ate. Unfortunately they do not realize that in such instances the positive reactors are specific immunological reactions representing homologous antigenic relationships which exist among various food groups. Thus, for example, a patient with a positive reaction to lobster may also give one to crab and shrimp even though they have never eaten the latter two. This is because these 3 seafoods contain a common antigen; also, a positive reaction to green pea may also be associated with positive reactions to other legumes. Common or homologous antigens exist not only among food groups with close botanical relationship but also among inhalants like plant pollens. Unless these facts are appreciated, misinterpretation of positive skin reactions and subsequent institution of improper treatment will result.

It is not always easy to determine whether positive skin reactors are clinically important, especially in the absence of confirmatory historical data. Under those circumstances, the patient should eliminate the positive food reactors for a limited period—perhaps a

month—and then add them one at a time in large amounts for at least 3 day periods. If no symptoms follow, one can then assume that particular food to be innocuous, so that it can be included in the diet again. Failure to institute this type of diet trial, with specific instruction as to its duration and the foods to be added, accounts for the occasional instance of undernutrition and avitaminosis in allergy patients who had been told to eliminate all positive food reactors but were given no instruction for how long. Proper care would prevent such occurrences and would also reduce or eliminate many unnecessary food restrictions. If diet trial is to be used at all, it should be carried out properly.

We often see patients, usually adults, who were given a trial diet for 2 or 3 days instead of 7 or longer. Single foods then were added daily instead of every 3 or 4 days and when there seemed to be no change in symptoms, it was assumed that foods were unimportant. Diet trial often can be valuable, especially in patients with urticaria, gastro-intestinal allergy or migraine, but only if it is carried out for a long enough period to determine whether the individual foods tested have any clinical significance. Unless this is done, one can lose the helpful advantage which this method of treatment can offer. These are the treatment failures which make the rounds of physicians' offices and are fertile soil for the psychosomaticist.

Elimination of inhalant allergens such as those from feathers or animal contacts or wool, offer perhaps less opportunity for error than do foods. A classical example of improper elimination is for an asthmatic patient sensitive to feathers to eliminate her own feather pillow but not that of her companion in the same bed, or to continue to make up beds containing feathers in other rooms. This is similarly true of animal contacts. For the parents to get rid of a cat or dog in their own home but allow their asthmatic child to play in other homes where such animals are present, obviously defeats the purpose of the treatment. Complete elimination of the offending inhalants at all times is essential to the best therapeutic results. This usually is possible with such inhalants as feathers, animal, wool, silk or cottonseed.

Tobacco smoke often offers a problem. While it is not always certain whether the effect of tobacco smoke upon allergy symptoms is due to specific sensitization or to its nonspecific irritating effects, nevertheless this agent can be a potent source of trouble in patients with allergic conjunctivitis, rhinitis or asthma. I have seen many asthmatic children whose attacks have been initiated by exposure to the tobacco smoke of their unsuspecting parents, either at home or while riding in an automobile with all windows closed. Adults are more conscious of such irritation and can take steps to avoid contact with the smoke, but this is not true of children; even if it were true, they would be unlikely to bring it to the attention of their parents. By stricter attention to such elimination the comfort of these patients can be greatly enhanced.

As previously indicated, elimination or avoidance of contact usually is difficult with such important inhalants as house dust, pollens or molds. As a consequence, patients are given injections of these extracts for purposes of desensitization. House dust undoubtedly is a most important allergenic excitant, and many patients are highly allergic to it. But by the same token, more abuses are committed in its name than perhaps with any other allergen. A positive skin test to house dust extract, often in moderate or marked degree, is a common finding in allergic patients. Its presence is an immediate

signal to the attending physician to begin giving injections of house dust extract without any attempt to ascertain the clinical significance of the positive reaction and often without proper precautions being instituted to determine the proper dosage. While house dust is to some extent irritating to most people, even those who are nonallergic, it does contain a specifically active allergen of undetermined chemical nature. Although it is not always easy to determine the clinical importance of a positive skin test to house dust, nevertheless, whenever possible, an effort should be made to find this out before instituting treatment. Sometimes, as in the case of housewives, one can obtain the history upon inquiry that house dust contact initiates or aggravates symptoms, or that removal of the patient from her home environment is followed by striking improvement with recurrence upon her return. Such evidence of its etiologic importance strongly suggests clinical sensitivity to house dust and warrants attempts at dust desensitization. But unfortunately such information is either lacking, especially in children or in males, or no attempt is made to elicit it by the attending physician before the injections are begun. As a consequence, many abuses occur. These could be avoided if the indication for its use as well as the ultimate goal of such treatment is properly understood. To institute injections merely because the skin test is positive is not good therapeutics. It is important in such instances to keep in mind *that one is treating a patient and not a positive skin reaction.* Furthermore, one should not place entire reliance upon the injections without also trying to minimize contact with the offending allergen. It is difficult enough to raise the tolerance of individuals to contact with even moderate amounts of house dust by means of desensitizing injections. But to give patients such injections and at the same time allow them to have contact with large amounts of dust obviously is wrong. Such patients should try to minimize their dust contact by elimination of dust-bearing furniture and rugs, by covering pillows and mattresses with dust-proof covers, by the use of wet-mops or of Dust-Seal or by similar measures. Institution of these measures will help considerably in reducing the amount of dust contact and undoubtedly will make the injections more effective.

When we consider the administration of the dust extract itself and of the dosage used, we find an especially common source of treatment abuse. Much of this can be ascribed to a misunderstanding either of the principles of desensitization or of the treatment aims in such patients. Desensitization in a sensitized guinea pig can be accomplished quickly by the injection of a large sublethal shocking dose of antigen. A slower and safer method is by the repeated injections of progressively increasing doses. These in themselves do not produce shock, but they combine with the anaphylactic antibody so as to remove the sensitization —hence the term desensitization. The first method of inducing sublethal shock obviously cannot be used in humans; hence the safer second method of giving spaced injections in increasing amounts must be employed. One should realize, however, that the latter method does not work in the human in the same manner as in the lower animal, nor are the principles involved the same. The reagin or allergic antibody in man differs from the anaphylactic antibody of the artificially sensitized guinea pig in that it is not neutralized by its specific antigen. In fact, although the exact mechanism involved is unknown, it is believed that antigen injections given for desensitization purposes in human allergy (*e.g.*,

hay fever) provoke the formation of another antibody, called the blocking antibody. This in turn interposes itself between the allergen and reagin and thus prevents or blocks the occurrence of the allergic reaction. True desensitization therefore is much more difficult in the natural allergies of the human than in the artificially sensitized animal. It takes longer and, in fact, may never be fully accomplished. Actually the important goal of treatment should be to attempt to lessen the sensitization present (hence the term *hyposensitization*) so that the patient can withstand ordinary amounts of contact with the offending allergen. This can best be accomplished by the repeated injections of small doses of the extract within the limits of the patient's tolerance.

The size of the initial dose in treatment often is based upon clinical experience, but additional information can be supplied by the skin test reaction to the allergen used. If the reaction is marked in degree, the initial dose should be small and subsequent doses increased less rapidly than when the skin test is slight or moderate. The extent of the increase and the interval between doses is determined by the degree of local reaction to the previous dosage and the absence of constitutional reactions. The shorter the interval the greater the tendency to reaction—hence, unless there is good reason to the contrary, a 5 to 7 day interval is preferable. Too large dosage given at short intervals only leads to large local and constitutional reactions. This not only adds to the patient's discomfort but also interferes with the process of hyposensitization and defeats the purpose of the treatment. Some physicians still have the impression, gained no doubt from the use of bacterial toxins and vaccines, that the larger the dose and greater the reaction, the more antibody is stimulated and the better it is for the patient. This is not true of allergy patients, in whom it works just the opposite way. Failure to realize this is a frequent source of treatment abuse in allergy practice. This applies especially to house dust extract. We frequently see patients with allergic rhinitis or asthma or atopic dermatitis who have been receiving large doses of concentrated house dust extract sometimes as often as twice a week with persistent symptoms often in greater intensity. All we have to do in such instances is to discontinue the injections. The improvement which follows this negative procedure sometimes is so striking that we are given credit unjustifiably for relieving the patient, perhaps because of certain medication given for symptomatic relief. As a matter of fact, all that we did was to eliminate a treatment which was proving harmful rather than helpful. Many of the benefits which patients derive from various so-called asthma cures, or from going to various resorts or spas undoubtedly are due in part to their removal from the harmful effects of injections which served only to prolong their symptoms.

Aside from this prolongation of their disease, this kind of overtreatment occasionally may bring about more serious effects. We not infrequently see young asthmatic children receiving desensitizing injections of house dust extract who give a history of one or more severe asthmatic attacks followed by so-called "bronchopneumonia". The latter actually represented pulmonary allergic shock reactions to an overdosage of house dust extract, because they no longer recurred when the injections were discontinued. I have seen young asthmatic children who were given injections of the concentrated extract 2 or 3 times a week at the outset for purposes of "desensitization". As reactions in adults sometimes follow small doses of highly dilute ex-

tracts, one can appreciate the amount of damage which can follow injections of such abnormally high doses. Obviously, such patients would have been much better off without any treatment at all. It therefore is exceedingly important that the physician make sure that dust-sensitive patients are not receiving injections that aggravate their condition. This can be ascertained by discontinuing the injections or by substituting normal saline for several weeks to see whether or not symptoms continue.

What has been said of dust injections applies also to pollen desensitization, although to a somewhat lesser degree, because reactions to pollen overdosage are more noticeable. They are more acute, appear within a short time after the administration of the extract in an individual who has been symptom-free at the time of the injection, whereas the reaction to dust injections usually is more delayed and they are often given to a person who may be having active symptoms (*e.g.*, asthma) from various causes. But when the pollen injections are given during the hay fever season, they too may cause aggravation of already existing symptoms unless this is recognized by the attending physician and appropriate measures instituted for their prevention. If there is any suspicion of increased effects, it is better to discontinue the injections or reduce the dose considerably, because a constitutional reaction to pollen injections may so upset the patient as to continue his symptoms for the balance of the season. From long experience in treating hay fever patients, I am certain that aggravation of symptoms in some hay fever patients is brought about unknowingly by overtreatment and may be a potent source of treatment failure. This, naturally, is discouraging to a patient who has been faithful in taking a long course of injections only to get poor results because of overdosage. It is little wonder that many prefer the use of symptomatic agents such as the antihistaminics. Therefore, in utilizing pollen therapy, whenever in doubt as to dosage increase, it is better to reduce the dose rather than risk a reaction especially during the season; in fact, it probably is good practice for the inexperienced to discontinue the injections at the onset of the hay fever season, especially in patients who are readily susceptible to constitutional reactions.

Another agent which provides a frequent source of treatment abuse in allergy patients is the bacterial vaccine. This probably is more extensively used in the treatment of nasal and bronchial allergy, particularly chronic asthma, than house dust extract. Perhaps even more evils are committed in its name than in that of the latter. One reason for this is that we are not sure whether vaccines produce their beneficial effects because a specific bacterial sensitization exists or through nonspecific influences. While there is ample clinical evidence of specific sensitization to bacteria or their products, there is no good scientific method to make this determination—neither a satisfactory skin test nor means of antibody determination. Hence, in most patients the use of vaccines is purely empirical or is based upon the results of a clinical experience which is not always too reliable. For example, injections of both bacterial vaccines and house dust extract frequently are given to asthmatic patients with little or no attempt being made to ascertain their therapeutic indication. This is even harder to do for vaccines than for house dust. A history of frequent colds preceding the onset of the attack may be useful, although one must make sure that such "colds" actually are infections and not attacks of allergic rhinitis from nonbacterial

causes. Vaccine therapy often is used in these patients as a preventive measure against colds. Since the common cold is considered to be due to a virus, the rationale of such therapy obviously is questionable.

Despite these handicaps and uncertainties, vaccine therapy judiciously employed undoubtedly can be helpful in many allergy patients. But, here again the spectre of overdosage raises its ugly head. We have seen many patients, especially children, who were given as much as 1 cc. of concentrated stock vaccine as often as twice a week despite the fact that each injection caused large local reactions. These were overlooked or ignored by the attending physician, perhaps with the mistaken notion that they were good for the patient. As mentioned in connection with dust injections, many of these patients began to improve as soon as the injections were discontinued, thus proving their harmful effects. Asthmatic patients, and especially children who are truly bacterial-sensitive, are rather susceptible to reactions even from small doses of vaccine. As with house dust, I have seen children with pulmonary shock reactions in the form of bronchopneumonia which resulted from overdosage of bacterial vaccine and which went unrecognized by the attending physicians. In several instances the parents brought their children to me because the family physician insisted on continuing these "cold shots" despite induction of annoying and at times severe asthma following their injections. Obviously such action is unwarranted. I cannot stress too strongly, therefore, the importance of care in the administration of bacterial vaccines in allergic patients. Recently, in order to avoid these reactions, we have been giving the vaccine intracutaneously in small doses and believe them to be much more effective in avoiding reactions, especially in children. In some instances it has been necessary to dilute the vaccine to as much as a 1 to 10,000 dilution to avoid reaction, but given in this manner and with due care, it may be quite helpful. In fact, bacterial vaccine therapy generally can be a useful addition to our therapeutic armamentarium if used in the proper manner to avoid disturbing and aggravating reactions.

What has been said about extracts of house dust and pollens and about bacterial vaccines also applies generally to treatment with extracts of such other inhalants as atmospheric molds, animal danders, tobacco and wool. Improprieties are much less frequent both because these agents are employed a great deal less in treatment, and also because, except for animal danders, the others are generally poor antigens and seldom induce constitutional reactions.

Some of these agents are used unnecessarily in treatment or at least without proper appreciation of the possibilities of success. As in the case of feathers or wool or animal danders, it is superfluous to try to "desensitize" patients to these allergens if they can be eliminated from the patients' environment. Even if the latter were not completely possible, one should remember that feathers, tobacco, silk and wool make poor antigens and will be unlikely to produce much desensitization unless given over a period of years, although even then the effect seldom is marked. For example, we have treated patients with allergic coniunctivitis or rhinitis from tobacco smoke for as much as 3 to 6 years with only moderate improvement in tolerance. In the case of cottonseed and animal danders, it is even more difficult, even though those extracts are better antigens. I have treated one laboratory worker sensitive to rat hair regularly for more than 5 years without

improving him sufficiently to enable him to handle rats without getting asthma. In another physician sensitive to rabbits, it required about 5 years of injections of rabbit hair extract to render him tolerant of slight contact with rabbits. When one considers that some hay fever patients are given injections of a good antigen like pollen for 10 or even 15 or 20 years before improving their tolerance sufficiently to withstand ordinary contact, one should not expect any better results with such allergenic agents as house dust, animal danders, and others. For that reason, such so-called desensitizing treatment should not be attempted in allergic patients unless there is good clear-cut indication verified by specific skin tests and, whenever possible, good clinical evidence. Furthermore, both the physician and the patient should realize the necessity for long-continued treatment and be aware of possible treatment failure. That is an important objection to the use of the shotgun mixtures containing extracts of house dust, feathers, wool, cottonseed, vaccine and others, which are dispensed by some laboratories and at times, even, by some allergists. These are hodge-podge mixtures of agents, some of which, as already indicated, are poor antigens unlikely to have much desensitizing influence. If these agents must be used, and except for dust, vaccine, pollens and molds, the indications are comparatively infrequent, it is much better to use them individually, even though it necessitates giving 2 or 3 injections to the patient at a single sitting.

So much, then, for treatment with food and inhalant allergens. These constitute the bulk of the treatment improprieties which require emphasis. The preceding discussion applies particularly to the curative treatment of already established allergic disease regardless of whether the therapy is administered by the general practitioner or by the specialist. I should like now to discuss briefly some treatment improprieties which, if corrected, would serve either to prevent the aggravation of already existent allergic disease or prevent the development of new sensitizations. One example is the advice still given by some practitioners to the parents of asthmatic children to "let the child grow out of his asthma." We see the harmful effects of such advice in those children of 11 or 12 with the typical barrel-shaped emphysematous chests as big as that of a senile chronic asthmatic. This certainly could have been avoided if the parents had been given the proper advice originally and preventive treatment instituted. The necessity for prolonged treatment in the absence of immediately visualized good results, naturally is discouraging to impatient parents, but it still is preferable to a serious chest deformity that might cripple the child for the rest of his life. If this were explained to the parents, I am certain they would not hesitate to continue preventive treatment.

Patients with nasal allergy offer another example of treatment neglect. To treat their condition by local application or instillation alone without attempting to find the basis for these symptoms is to court a possible asthmatic complication. Fortunately, more rhinologists recognize this and act accordingly. However, this sometimes is neglected in patients with nasal polyposis. It generally is recognized that mucous nasal polyps are nearly always allergic in origin. To remove them and not do anything to prevent their recurrence certainly is unwarranted. We have had very good results with allergy treatment in such patients and have been able to prevent recurrences for much longer intervals than before such treatment was instituted. Every

patient with frequently recurring nasal polyps therefore should have the benefit of allergy investigation and treatment.

Time does not permit of adequate discussion of treatment improprieties in patients with allergic dermatoses. I have already emphasized the failure to use proper diet trial in patients with urticaria. It certainly is worth an attempt before concluding that the condition is upon a psychosomatic basis. I should like also to stress the importance of proper allergy treatment for patients with allergic eczema or atopic dermatitis. For the dermatologist to treat this condition as though it were a local disease and neglect its allergic basis is just as reprehensible as it is for the rhinologist to treat allergic rhinitis in similar fashion. The fact that the treatment of these patients even by accepted allergy methods has failed to bring about relief is no reason for eliminating it in all cases. As a result of clinical and experimental studies, we recently have shown that many of these treatment failures arise through lack of realization that inhalant allergens may be as important in atopic dermatitis as in asthma and that if such patients were treated as though they had asthma of the skin, the end-results would be as good and often better than in bronchial asthma. Complete cooperation between the allergist and the dermatologist in the treatment of atopic dermatitis will bring about better results in such patients.

And now I want to discuss some measures which can be taken to prevent the initiation of newly established sensitization, particularly in relation to the allergic reactions which follow the use of various antibiotics such as penicillin and the sulfa drugs. It has been shown, especially by Rich, that the marked increase in the incidence of such collagen diseases as periarteritis nodosa coincided with the introduction of the sulfones into clinical use and that lesions resembling periarteritis nodosa could be produced in lower animals by injection of these drugs. Reactions to penicillin and similar antibiotics are becoming increasingly frequent and more severe. I have seen several patients with chronic recurrent and seemingly intractable urticaria of many months' duration which began after an injection of penicillin, given perhaps for a mild sore throat or cold. No one certainly would want to advocate the abolition of these valuable drugs from therapeutic use. But their use should be restricted to conditions which require it rather than for mild trivialities which could be treated by simpler and less harmful remedies; otherwise, they will not only lose their potency but they also will be responsible for the onset of new sensitizations or diseases that might prove crippling or even fatal. This should be remembered whenever an injection of any kind of foreign agent is given, be it penicillin or typhoid vaccine. I have seen allergy patients who attribute the onset of their asthma or urticaria or occasionally of hay fever to a severe reaction following prophylactic typhoid or other bacterial vaccines. If asthma can follow pertussis or pneumonia, it certainly also could follow a severe reaction to bacterial vaccine. One always should be sufficiently careful therefore in administering prophylactic vaccines or antibiotics to prevent unnecessary reactions or to modify subsequent dosage accordingly.

Finally, I want to discuss briefly some treatment abuses in relation to the new allergy "wonder drugs", the antihistaminics. Obviously, considering the voluminous literature on this subject, no attempt will be made to discuss them in detail. But considerable confusion exists in the minds of many practitioners as to their indica-

tions and value. This is readily understandable when one considers the large number of different compounds on the market and the extravagant claims made for them, sometimes by reputable workers who are carried away by over-enthusiasm and by a myopic interpretation of the clinical results obtained. Their use is based upon the supposition that they neutralize or inactivate histamine which is thought to be the sole cause of the allergic reaction. Although it is generally believed that histamine or a substance resembling it probably results from an interaction between allergen and allergic antibody or is released from the cells following the reaction, we are not altogether certain that it is the sole or even the important cause of the ensuing symptoms. Furthermore, the antihistaminics act only upon circulating free histamine and not on intracellular histamine, which explains why they are more effective in the more acute allergies like urticaria or hay fever than in chronic asthma or atopic dermatitis. While the antihistaminics neutralize histamine *in vitro*, we cannot always be sure whether the results obtained in some patients may not be due to some of their side-reactions, notably those of sedation or of their atropine-like effects. It has been shown, too, that the histamine-neutralizing ability of any particular product either *in vitro* or in the guinea pig is not necessarily paralleled by its clinical effect. Above all, it must be remembered that they provide only symptomatic relief and have no curative effect. Under those circumstances, one should realize that these drugs are not panaceas for all allergic ills. They have, however, a definite place in allergy treatment, and if used judiciously under proper indications, they undoubtedly can be helpful to many patients, especially those with the more acute allergies, like urticaria or serum or penicillin reactions. They also can be beneficial in hay fever, providing the patient receives specific pollen therapy at the same time. Sole reliance upon their use in this condition is courting a subsequent asthmatic complication as well as delay in building up the patient's tolerance. Their indiscriminate use in patients with mild allergy complaints without due regard for their possible untoward effects also is inviting disaster. Let me therefore emphasize again that the antihistaminic drugs have been an exceedingly valuable addition to our therapeutic armamentarium, but unless used under proper circumstances and with the exercise of due caution, they can prove to be a two-edged therapeutic sword.

Conclusion. In the preceding discussion, the author has attempted merely to point out those pitfalls in allergy practice which make treatment abuses or improprieties more possible. No one group of physicians or specialists is singled out for blame. Allergists, including this author, are as guilty as others, but because of their extensive experience with allergy patients, they can more easily recognize their errors and mend their ways. It is the hope of the author that the foregoing discussion based upon an extensive clinical experience with allergy patients perhaps will help clear up some misconceptions of the purposes, aims and methods of allergy treatment and will help practitioners in the proper treatment of allergy patients.

SIGNIFICANCE OF ARTERIAL BLOOD SUGAR IN SPONTANEOUS HYPOGLYCEMIA

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There is no information available on the variations of dextrose concentration in the arterial blood during hypoglycemic manifestations. This is probably due to the routine of obtaining venous blood for sugar determinations in the diagnosis of diabetes mellitus as well as in gauging the effectiveness of treatment in this disease. While in diabetes the venous blood may be valuable as an index of sugar utilization in the tissues, in hypoglycemia the arterial blood appears to be of greater significance since it is the arterial and not the venous blood that carries sugar to the tissues. For this reason the present study was undertaken. Its objective has been to determine the distribution of glucose between the arterial and the venous blood during the clinical episodes of spontaneous hypoglycemia.

Material and Methods. Twelve subjects have been used for this study. Two (Cases 1 and 12) had a history of severe hypoglycemic manifestations (but no convulsions and no loss of consciousness) for over 10 years; one (Case 5) had moderately severe symptoms for years, and on 3 occasions attacks with loss of consciousness; 6 (Cases 3, 4, 6, 7, 10, 11) had mild and moderately severe symptoms for periods ranging from 6 months to several years; 2 (Cases 2, 9) as a result of treatment had been almost symptom free for over 3 years; 1 (Case 8) had grand mal epilepsy for over 4 years. Mild adrenocortical insufficiency was established as the cause of hypoglycemia in Case 7, and chronic alcoholism with liver damage in Case 3. The etiology of the syndrome could not be determined in the remaining patients, but some of them, in particular Cases 1 and 12, still remain under observation as possible cases of hyperinsulinism due to pancreatic pathology.

The following experiments were carried out:

a) Oral glucose tolerance tests. Twelve to 14 hours after the last meal the patients were given 100 gm. of glucose in 250 cc. of water flavored with a small amount of citric acid. Blood samples were drawn at fasting and for 6 to 7 hours after ingestion of glucose at hourly or shorter intervals.

b) An intravenous tolerance test was done in Case 1 by injecting 50 cc. of 50% solution of glucose in 3 minutes. The sugar determinations were made at fasting and for 6 hours thereafter at hourly or half hourly intervals (Fig. 1 c). In addition, 5 determinations of the arterial sugar were made during the first 29 minutes after the administration of glucose.

c) In Case 1 the arteriovenous dextrose distribution was also determined during 2 fast tests. On one occasion when mild symptoms developed after a fast of 15 hours, the blood samples were drawn every hour for a period of 5 hours (Fig. 2, 1 d), and on another occasion with severe symptoms occurring spontaneously after a fast of 16 hours the blood samples were obtained every ½ hour or more often for 3½ hours (Fig. 2, 1 e).

Both venous and capillary blood were drawn, the venous at the bend of the elbow and the capillary from the fingertips. Analyses were carried out as soon as the blood specimens were obtained. True glucose in the

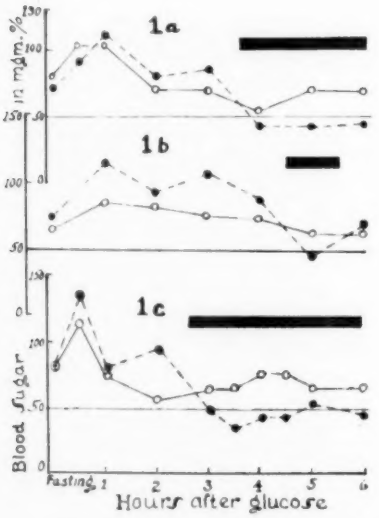
* Presented at the Annual Meeting of the American Diabetes Association in San Francisco, June 25, 1950.

venous blood was estimated by the Folin-Wu method following protein precipitation according to Somogyi[24], and in the capillary blood which was aspirated directly from the fingertip into a 0.1 cc. pipette, by the method of Lauber and Mattice[14]. The Lauber-Mattice method was checked against the macromethod by making measurements of the sugar content by both methods simultaneously in 20 specimens of venous blood obtained from individuals with a wide range of blood sugar concentrations (normal subjects and hypoglycemic as well as diabetic patients). The results of this preliminary study (Table 1) showed a good agreement between the 2 methods. The correlation was perfect in 8 determinations; a divergence of 1 to 3 mg. per 100 ml. was found in 6 instances and a divergence of between 5 and 9 mg. per 100 ml. in the remaining 6 measurements (that is, in only 30% of analyzed specimens). Larger discrepancies between the 2 methods were noted when blood specimens were not analyzed immediately upon withdrawal.

In the course of oral tests 14 to 22 samples were taken from each subject; 12 and 18 were drawn during spontaneous hypoglycemic episodes. The maximum number of samples obtained in one observation was 26 in the course of an intravenous tolerance test (Case 1).

In all observations of the present study the patients were watched carefully for the occurrence of hypoglycemic manifestations in order to obtain a correlation between the laboratory findings and the clinical features of hypoglycemia.

Results. For economy of space and clarity of presentation the data obtained are not tabulated but given in graphic form. The presence of clinical hypoglycemic manifestations is indicated by the solid black bar. Fig. 1 represents oral and intravenous tolerance tests, and Fig. 2 the fast tests in Case 1. Fig. 3 gives oral tolerance tests in which a



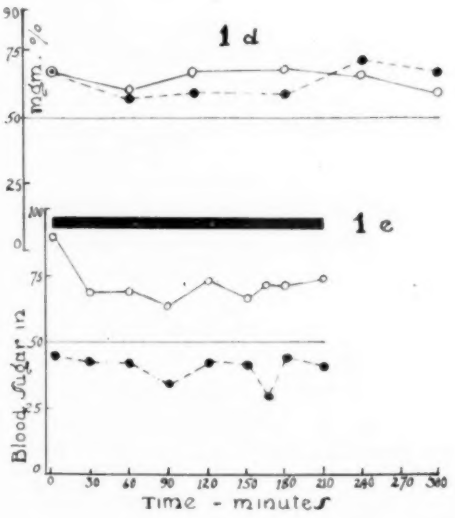


FIG. 1—Two oral glucose tolerance tests (1 a and b) and an intravenous tolerance test (1 c) in Case 1. The solid line curves with circles designate the venous and the broken line curves with dots the capillary true blood sugar concentrations. The solid black bars indicate the occurrence of clinical hypoglycemic manifestations. A straight line is drawn with each set of curves to show the critical blood sugar value of 50 mg. per 100 ml. Note the correlation between the clinical symptoms and the arterial hypoglycemia.

FIG. 2—Two fast tests in Case 1 (1 d when symptoms were very mild and 1 e when they were almost unbearable to the patient). Note that in the course of the severe hypoglycemic episode (1 e) the venous blood sugar values were well above the base line of 50 mg. per 100 ml. while the arterial blood sugar was at critically low levels. Also note the persistence of the arterial hypoglycemia during the severe attack (1 e).

TABLE 1.—COMPARISON OF METHODS FOR BLOOD SUGAR DETERMINATIONS USED IN PRESENT STUDY

No. of Venous Blood Sample	*Blood Sugar Mg./100 ml.*		*Difference Between Micro- and Macromethod Mg./100 ml.*
	Macromethod	*Micromethod*	
1	270	270	0
2	263	268	+5
3	250	250	0
4	235	235	0
5	222	222	0
6	200	191	−9
7	200	200	0
8	178	178	0
9	157	148	−9
10	154	154	0
11	150	145	−5
12	145	143	−2
13	143	143	0
14	143	148	+5
15	100	98	−2
16	95	98	+3
17	76	77	+1
18	69	66	−3
19	38	30	−8
20	24	30	+6

TABLE 2.—REVERSED ARTERIOVENOUS GLUCOSE DIFFERENCES IN MAN COLLECTED FROM LITERATURE

Clinical or Experimental Condition	*Author*	*Magnitude of the Reversed A-V G.D. Mg./100 ml.*	*Remarks*
1. Fasting Normals	Friedenson, M., *et al.*[8]	−8 and −24	2 subjects
	Langner, P. H. & Fies, H. L.[13]	Up to −10	17 out of 32 determinations
Diabetics	Lawrence, R. D.[15]	−4 and −9	2 out of 5 determinations
	Rabinowitch, I. M. & Bazin, E. V.[21]	Up to −22	11 determinations
	Landau, A., *et al.*[12]	Up to −30	7 out of 83 determinations
	Mosenthal, H. O.[17]	Up to −15	4 out of 27 determinations
Advanced starvation	Fliederbaum, J., *et al.*[5]	−20 to −50	7 out of 30 subjects
2. Diabetics, 2 hours p.c.	Mosenthal, H. O.[17]	Up to −26	5 out of 20 determinations
3. Diabetic coma	Rabinowitch, I. M.[20]	−12 to −29	3 cases
4. After oral administration of glucose			
Normals	Friedenson, M., *et al.*[8]	Up to −24	
Diabetics	Rabinowitch, I. M.[20]	−8 and −18	2 cases
	Landau, A., *et al.*[12]	Up to −64	
	Bose, J. P.[1]	Up to −19	
Liver disease	Friedenson, M., *et al.*[8]	Up to −32	5 determinations
5. After insulin			
Normal Subjects	Friedenson, M., *et al.*[8]	Up to −21	
	Norgaard, A. & Thaysen, T. E. H.[18]	Up to −11	In 2 out of 6 insulin tests
Diabetics	Lawrence, R. D.[15]	Up to −20	7 out of 9 patients
	Landau, A., *et al.*[12]	Up to −17	18 cases
Advanced starvation	Fliederbaum, J., *et al.*[5]	Up to −13	
6. After adrenalin			
Jaundiced patients	Gjertz, A.[9]	Up to −34	
Advanced starvation	Fliederbaum, J., *et al.*[5]	Up to −20	

negative arteriovenous glucose difference (A-V.G.D.) of 10 mg. per 100 ml. or more was recorded, and Fig. 4 those in which the negative A-V.G.D. was of lesser magnitude.

From the graphs it may be seen that a positive A-V.G.D. with the arterial blood sugar higher than the venous was present during the first 2 or 3 hours of all the oral tolerance tests and the first 2 hours of the intravenous test. In the majority of observations with the use of oral tolerance tests, the onset of hypoglycemic episodes occurred after the 3rd hour, and only in 2 observations (Cases 4 and 6) in the 2nd hour of the test. In the intravenous test it was noted in the 3rd hour (Case 1 e). The onset of clinical manifestations coincided with or was close to a marked decline in the arterial blood sugar content, except in 2 observations (Cases 6 and 11) in which the fall of the glucose content in the venous blood overshadowed that in the arterial blood.

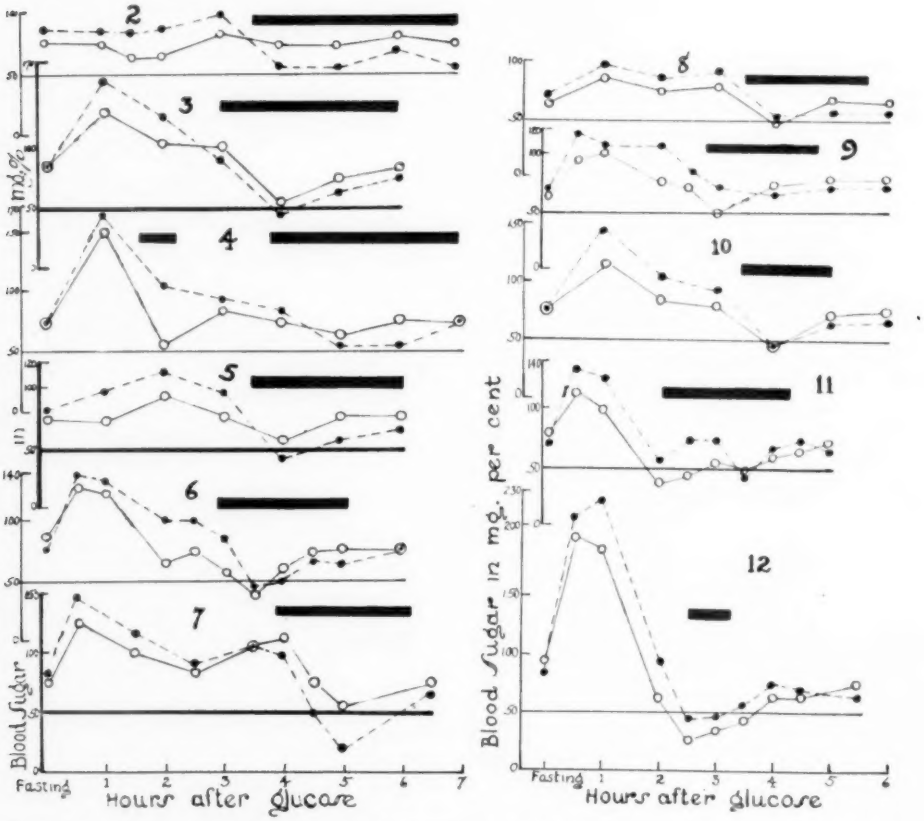


FIG. 3.—Oral glucose tolerance tests with a reversed A-V.G.D. of minus 10 mg. per 100 ml. or more. Note the good correlation between clinical symptoms and arterial hypoglycemia except in Case 6. Severe symptoms developed in Case 7 in which the decline in arterial blood sugar was greatest.

FIG. 4—Oral glucose tolerance tests with a reversed A-V.G.D. of minus 9 mg. per 100 ml. or less. In Cases 9 and 11 onset of symptoms was better correlated with the venous than the arterial blood sugar. In Case 12 symptoms were absent during the steep decline in blood sugar and developed only when the blood sugar dropped to critically low levels.

During the mild attacks the dextrose concentration in the arterial blood was within the limits of 41 to 87 mg. per 100 ml. and in the venous blood from 40 to 102 mg. per 100 ml. Case 12 was rather unusual in that only moderate symptoms were present for less than 30 minutes at the time the venous blood sugar ranged from 29 to 40 mg. per 100 ml. and the arterial from 44 to 50. The arterial blood sugar content during the severe attacks (Cases 1 and 7) was most striking in that it fell below 50 mg. per 100 ml. while that in the venous blood ranged from 54 to 90. Moreover, in Case 1 during the severe hypoglycemic episodes the arterial blood sugar for hours showed little or no tendency to rise (Curves 1 a, c and e).

In the major proportion of our observations the clinical hypoglycemic manifestations were accompanied by a drop in the arterial blood sugar concentration below that in the venous blood, with production of a negative A-V.G.D. In the tolerance tests this phenomenon is well visualized by the crossing of arterial and venous curves at the onset, or close to the onset of hypoglycemic episodes. A reversed A-V.G.D. failed to develop in only 3 observations. In one very mild attack the difference was wiped out without becoming significantly reversed (Case 10). In Case 12 moderate symptoms coincided with distinctly low sugar values in both the arterial and the venous blood, even though the drop of the sugar content was greater in the venous than in the arterial blood. In Case 11 no significant decline in the arterial blood sugar was noted in the early stage of the hypoglycemic episode.

In the mild attacks the A-V.G.D. was reversed down to minus 20 mg. per 100 ml. in 26 determinations and down to minus 22 mg. per 100 ml. on one occasion. A positive A-V.G.D. ranging from plus 3 to plus 15 mg. per 100 ml. was recorded on 5 occasions and a higher one of plus 29 and 31 mg. per 100 ml. in 2 instances, namely, in Cases 6 and 11 in the earlier phase of the hypoglycemic episode. During the severe attacks the A-V.G.D. was uniformly negative and ranged from minus 12 to minus 45 mg. per 100 ml. in 22 determinations, of which only 4 were of less magnitude than minus 20 mg. per 100 ml. Such large negative differences were observed in the severe attacks occurring in the course of tolerance tests (Case 7) as well as spontaneously (Observation 1 e).

Discussion. Analysis of the data presented brings out several points of interest. First, it is evident that oral glucose tolerance tests as commonly confined to 2 or 3 hours of observation and to determinations of the venous blood sugar alone are of little value in the diagnosis of hypoglycemic states. A low flat curve during the first 2 or 3 hours of the test such as recorded in Cases 2, 5, 8 and 9, is indicative of spontaneous hypoglycemia but does not definitely establish the diagnosis of this condition. The clinical symptoms develop after the 3rd hour of the test in the majority of patients.

The second point of interest concerns the various theories that have been advocated to explain the discrepancies between the clinical symptoms of hypoglycemia and the blood sugar values. Among them particular favor has been gained by the concept according to which symptoms develop as a result of a rapid fall of the blood sugar from high levels. However, in the patients herein presented symptoms occurred without a marked initial rise in the blood sugar during the oral tolerance tests as well as during the fast tests. The only patient in this group who exhibited a rapid rise of the blood sugar to over 200 mg. per 100

ml. followed by an equally rapid drop (Case 12) failed to show severe hypoglycemic manifestations. On the other hand, in the course of the intravenous tolerance test in Case 1 within 8 minutes after the dextrose injection the arterial blood sugar rose to 216 mg. per 100 ml. and within the subsequent 52 minutes it fell rapidly to 80 mg. per 100 ml. A similar rise with an appreciable drop occurred in the venous blood, and yet the patient exhibited no hypoglycemic manifestations during these steep declines in the blood sugar. Very mild symptoms coinciding with a fairly precipitous fall of the venous blood sugar were observed in only one instance, but moderately severe symptoms developed in this patient only around the time the curves crossed (Case 4).

The third finding of importance is the relationship between the clinical hypoglycemic manifestations and the decline in the dextrose concentration of the arterial blood. In most tolerance tests the onset of hypoglycemic episodes was reflected in the descent of arterial blood sugar curves toward more marked hypoglycemic levels than those in the venous curves. Moreover, the intensity of clinical symptoms appeared to be correlated with the degree of the arterial hypoglycemia as demonstrated by the fall of the arterial blood sugar below 50 mg. per 100 ml. during the severe attacks. In only one observation (Case 12) did moderate symptoms occur with distinctly low arterial (as well as venous) blood sugar values.

That low sugar concentrations in the arterial blood appear to constitute a characteristic feature of the hypoglycemic syndrome does not require much elaboration when it is realized that sugar is supplied to the tissues by the arterial and not the venous blood. However, the reversal of the A-V.G.D. in our observations is more difficult to reconcile with well established physiological facts.

Almost a century ago Chauveau[2], using the blood of horses and dogs, found that "sugar is always more abundant in the arteries than in their collateral veins"; the only exception were the veins which carry blood flowing out of the liver. From his findings he concluded that a proportion of arterial sugar disappears during the passage of blood in the capillaries and that the venous blood leaving all tissues except the liver "contains less sugar than the blood of the left heart".

The concept of the positive A-V.G.D. thus established by Chauveau was well substantiated by the demonstration that the difference grows larger with increases in the rate of utilization of sugar in the body, for instance after administration of glucose, insulin or both. It is also in harmony with the present knowledge of the intermediary carbohydrate metabolism which teaches that in the liver glycogen is broken down to glucose while in the muscle glucose does not appear as a degradation product of glycogenolysis.

There is, however, an extensive literature containing data on the occurrence of negative A-V.G. differences. In Table 2 are presented the results of such observations in man. Not included in the table are the negative differences found in fasting young diabetics by Griffiths[10] because of absence of detailed data in his paper. Of interest is the work of Gjertz[9] who in jaundiced patients given adrenalin found on occasions the whole venous curve to be lower than the arterial. As for studies in animals, Lépine[16], one of the early workers in this field, reported that not infrequently blood collected from the jugular, femoral and other veins contained more sugar than the arterial blood. He also stated that the negative A-V.G.D. "was noted by various experimenters but in view of its paradoxical appearance they considered it as an error of determination". With the use of

modern analytical methods Frank *et al.*[7] found more sugar in the femoral vein than in the corresponding artery of depancreatized dogs. They reported values ranging between minus 4 and minus 12 mg. per 100 ml. in the fasting state in 6 out of 9 determinations, and up to minus 17 mg. per 100 ml. after intraarterial administration of insulin. In monkeys given the intravenous dextrose tolerance tests, Wakeman and Morrell[30] recorded the crossing of arterial and venous blood sugar curves after the initial phase of hyperglycemia.

Among those who consider a negative A-V.G.D. to be an impossibility, Somogyi[25a,b,c] has recently expressed the opinion that large negative differences are due simply to analytical errors. The question may be asked, however, whether the existence of a negative A-V.G.D. may be denied on such grounds. A review of the literature reveals that not infrequently identical techniques were used by those who recorded negative differences as well as those who obtained only positive differences. The work of Cori[3], for instance, was done with the Hagedorn-Jensen method which is the same method that was employed by Frank *et al.*[7], Gjertz[9], and Fliederbaum *et al.*[5].

Somogyi also objected to the use of micromethods in studies of the A-V.G.D. because small amounts of blood employed in such methods introduce a dilution factor apt to vitiate the results. For this reason, following the suggestion of Lundsgaard and Moeller, he removed 1 cc. of capillary blood by having the subjects submerge their fingers in hot water of 45 to 50° for 5 minutes prior to collection of blood. It is, however, noteworthy that nearly all other investigators, including those who failed to record negative differences, were satisfied with the use of only 0.1 or 0.2 ml. of blood even when the blood was obtained directly from the artery[3] and that some of them applied micromethods to determinations of sugar in the capillary as well as the venous blood.

To be sure, those who recorded negative differences were aware of the difficulties in explaining their findings. While some of their results may have been within the margin of experimental error, the magnitude of the difference in a number of observations was well beyond the limits of analytical errors. Griffiths[10] stated: "In our work we have frequently obtained values for the sugar of the venous blood which exceeded those of the corresponding arterial blood by more than the experimental error involved in the determination". A similar opinion was voiced by Peters[8] and by Gjertz[9].

As for the disagreement between the finding of negative differences and the accepted physiological principles, the investigators felt compelled to assume that under certain circumstances the tissues may discharge sugar into the venous blood[5,8,10,15,17,20] even though they realized that this idea "is contrary to physiological conceptions of carbohydrate metabolism"[8]. Lawrence[15] suggested that in such instances the tissues retain temporarily the excess of sugar received from the arterial blood. Griffiths[10] on the other hand resigned himself to the recognition that "at the moment no completely satisfactory explanation of these negative differences is possible".

As mentioned earlier, we checked the methods we have used very carefully and consider our results to be free of analytical errors. We have used only 0.1 ml. of capillary blood, since our material was composed of patients with a variety of neuropsychiatric manifestations of hypoglycemia and it was considered unsuitable to have them submerge their fingers in hot water each time the blood was to be drawn. Such a procedure would have

introduced an emotional factor which by itself could cause a change in the blood sugar concentrations. From the experience of others we felt satisfied that the use of micromethods for determination of the capillary blood sugar is a safe and reliable procedure.

Assuming that the negative A-V.G.D. may on occasions be due to analytical errors inherent in the estimation of small amounts of glucose we have made assays which showed that in our hands the divergence between the methods used was less than 10 mg. per 100 ml. We have therefore grouped patients with a divergence of this type in a separate group (Fig. 4) even though we feel that the existence of a virtual negative difference in this group cannot be ruled out. We have grouped separately (Fig. 3) those who exhibited a negative difference of greater magnitude—up to minus 39 mg. per 100 ml.—and feel justified in assuming that these represent a definite reversion of the A-V.G.D. Moreover, we think it very significant that a positive difference was obtained in all our patients in the first 2 or 3 hours of the tolerance tests. It certainly would be absurd to consider the methods as reliable in the first phase and unreliable in the further course of the tests. We also ascribe great significance to the consistency with which the inversed A-V. G.D. was recorded during the hypoglycemic episodes.

Since the direction of carbohydrate transformations in the liver and the peripheral tissues may seem to invalidate the notion of a negative A-V.G.D., the question arises whether these phenomena represent the only 2 events concerned with endogenous production and flow of sugar in the body.

First, the recognition of glucose formation in the liver does not preclude the existence of other sources of sugar in the body. Before the essential position of the pancreas and the liver in the carbohydrate metabolism was established, for centuries it was believed that sugar which passed into the urine was produced in the kidneys. The interest in renal glucogenesis was revived in recent years by the work of Reinecke[22] who in the liverless or eviscerated rat recorded a higher sugar content in the renal vein than in the aorta and the vena cava. In subsequent studies[23] he demonstrated renal formation of sugar also in normal animals and its potentiation as a result of hepatectomy or evisceration. Of interest are the investigations of Diaz and Candeira[4] on variations of renal and peripheral blood sugar values in the course of glucose tolerance tests carried out in dogs, which seem to indicate that the kidneys are endowed with the ability of adjusting their sugar secretion to metabolic needs of the body as reflected in variations of sugar concentrations in the blood.

A large reservoir of glucose which may contribute to sugar enrichment of venous blood is contained in various tissues, particularly the skin and the muscles. In human skin Trimble and Carey[27] found true glucose in amounts corresponding to between 65 and 75 % of blood sugar concentrations, and Urbach[28,29] reported the dextrose content of human skin to average 58 mg. per 100 ml.

As for the flow of sugar in the body, the mechanisms associated with passage of glucose from the blood into the tissues remain undetermined. It is known that glucose upon entering the cellular metabolism can no longer be recovered in its free state, but the thesis that sugar which leaves the blood is immediately converted to carbohydrate intermediates fails to take into consideration the existence of the extracellular fluid compartment in the extravascular spaces. The concentration of sugar in the interstitial fluid equals more or less that in the

blood, but it is obvious that diffusion of sugar into tissue spaces must be dependent not only on its concentration in the circulating plasma but also on the equilibrium between the sugar concentration of the interstitial fluid and the carbohydrate composition of tissue cells. It is also obvious that the rate at which sugar penetrates the cell must be dependent on cellular capacity to absorb sugar and to incorporate it into the cellular metabolism. This makes it conceivable that on occasions the cells may be unable to consume all the glucose that is offered them by the circulating blood.

Such a situation is known to occur when the blood sugar is raised rapidly. Some years ago Folin *et al.*[6] demonstrated that after intravenous injection of glucose various tissues, especially the skin, contained almost as much sugar as the blood and that after the glucose concentration in the blood had declined below that of the tissues, the tissue sugar diffused back into the blood stream. Himwich and Fazekas[11] studied the absorption of sugar by the brain. They administered both glucose and insulin to produce a rise in the blood sugar followed by its quick decline and noted that in the hypoglycemic phase sugar passed from the brain into the blood stream. As a result more sugar was then found in the venous than in the arterial blood.

Back diffusion of glucose into the circulation resulting from a rapid rise in the blood sugar concentration cannot be invoked to explain the reversal of the A-V.G.D. in our observations since the reversal occurred after moderate increases in blood sugar values in the course of tolerance tests and in absence of preliminary hyperglycemia in the fast tests. However, the demonstration of back diffusion of sugar in itself is of great importance in that it implies a reversal of the normal direction of sugar flow toward the tissues whenever the cellular consumption of sugar becomes reduced or exhausted. It follows that a rapid increase in blood sugar values such as was produced in the above quoted investigations may result in, but is not the essential prerequisite for diffusion of glucose from the tissues or tissue spaces into the venous blood. According to Mosenthal[17] a comparatively moderate elevation of the blood sugar such as occurs in oral glucose tolerance tests produces a rise in tissue sugar that is adequate to reverse the direction of sugar diffusion during the hypoglycemic phase of the test.

Evidence is also available to suggest that intracellular sugar may participate in the phenomenon of back diffusion. Peters and Van Slyke[19] consider the passage of glucose into the cells as a reversible process and believe that while glucose may not be stored in cells in high concentrations it may well move out of the cells across the cellular membrane. In support of their thesis they quote the work of Stetson and Peters[26] who in the period of recovery from extreme hyperglycemia of diabetic acidosis found large negative A-V.G. differences and observed that amounts of glucose required to produce differences of such magnitude could not have come from interstitial fluids alone.

We have reviewed the literature on renal sugar formation and back diffusion of sugar into the circulation to indicate that variations in venous and arterial blood sugar values cannot be explained solely in terms of production of glucose in the liver on the one hand, and the inability of peripheral tissues to form sugar on the other. Since we cannot visualize the pathways through which sugar produced in the kidney could enrich the peripheral venous circulation, we are led to believe that the reversal of the A-V.G.D. recorded in our observations was produced by diffusion of glucose from tissues or tissue spaces into the

circulation. We also feel that this passage of sugar into the blood stream occurred in response to the fall of arterial blood sugar and that it represented an attempt on the part of the body to correct the critically low concentration of sugar in the arterial blood.

Summary and Conclusions. 1. Arteriovenous distribution of sugar was studied in 12 patients with a clinical history of spontaneous hypoglycemia. Determinations of true glucose were made in the course of oral and intravenous glucose tolerance tests as well as during spontaneous hypoglycemic episodes.

2. The relationship between the hypoglycemic manifestations and the blood sugar variations was carefully noted. The development and the intensity of hypoglycemic episodes were found to be well correlated with the level of the arterial blood sugar. The rate of fall of the blood sugar was not the deciding factor.

3. The glucose tolerance tests as currently confined to 2 or 3 hours of observation are inadequate to establish a diagnosis of spontaneous hypoglycemia. The hypoglycemic reactions become manifest when the tests are carried out for 5 hours or longer.

4. It is concluded that the study of the arterial blood sugar is of considerable importance for the diagnosis of hypoglycemic states. The use of venous blood alone may yield conflicting results.

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THE RELATIONSHIP BETWEEN SERUM PROTEIN FRACTIONS AND ANTIBODY NITROGEN RESPONSE IN DIABETIC PATIENTS*

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THERE is accumulating evidence that the loss of the body's protein stores both in animals[4,13,15] and in man[3,16] leads to a decreased ability of the tissues to produce antibodies. Furthermore, it has been shown that in diabetes mellitus with infectious complications the diminished antibody response bears a relationship to blood protein levels rather than to the fasting blood sugar[6].

The present investigation concerns itself with a correlation of the serum protein fractions with an immune antibody response in patients with diabetes mellitus. Such a correlation may be of use in characterizing those diabetics who are apt to be good antibody-producers, and hence perhaps better able to resist infections, in contrast to those who are poor risks when infected.

Methods and Materials. For this study 25 diabetic patients, who were hospitalized in the metabolic wards of the Philadelphia General Hospital, with infectious complications such as gangrenous toes, cystitis, or leg cellulitis, were selected. They were studied chemically and immunologically during a control period of 1 week and during a subsequent typhoid immunization period of 30 days. Each patient received subcutaneously 0.2 ml. of a standard typhoid vaccine at intervals of 10 days for a total of 3 injections. An average of 9 blood specimens were drawn from each patient at intervals during the immunization period. The resulting sera were analyzed by methods previously used[17] for albumin, globulin, and hemoglobin. In addition the gamma-globulin concentration was determined by the method of Jager and Nickerson[8]. The typhoid antibody-nitrogen concentration was assayed according to the technique developed by Heidelberger and Kabat[7] and applied to this particular antigen-antibody system by Gurevitch and Ephrati[6], but modified by using the typhoid "H" antigen† of Welch and Stuart[14] for the adsorptions. This bacterial antigen adsorbs antibodies against both flagellar and somatic surface antigenic components as demonstrated by experiments involving separate sera containing antibodies of the flagellar type only, the somatic type only, and both types together. The original technique was further simplified, in order to permit the necessary large number of determinations, by carrying out the antibody adsorptions and washings at room temperature, and by computing the protein nitrogen

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† This antigen was generously supplied by Lederle Laboratories, Inc., Pearl River, New York.

values from Evelyn photoelectric colorimetric readings following nesslerization[11]. Although these variations in technique tended to reduce the accuracy of the antibody determination when compared to a more fastidious method[7], the results were sufficiently reproducible for the purposes of this study.

The data for each patient are presented in Table 1. The values of the serum protein components for each individual represent for each component the mean of all determinations done on that person during the study. The antibody response with time of each patient was treated by the method of least squares to obtain the constants "a" and "b" given in the 2 columns at the right. These constants define the best straight line which will fit the individual's antibody-time response. They are used solely to determine the mean antibody response for groups of patients drawn from this sample of 25 diabetics, as will be elaborated upon later.

These patients were placed on a diabetic diet according to their ideal weights, averaging 2000 calories and 80 gm. of protein daily. Fasting blood sugars were determined routinely and liver function studies were made when indicated. Individuals showing evidence of liver damage were excluded from this investigation.

Results. For comparative purposes the patients were divided into 2 groups, based on the mean value of the individual's serum albumin concentration being less or greater than an arbitrarily chosen value of 4.00 gm. per 100 ml. of serum. This value is approximately the lower limit of normal for albumin levels in our experience with the methods used. The one group, comprising 12 patients and designated the low albumin group, had a mean serum albumin value of 3.40 gm. per 100 ml. The other group, the high albumin group of 13 patients, had a mean albumin value of 4.50 gm. per 100 ml.

The group data presented in Table 2 were utilized to prepare the plots of the antibody responses with time shown in Fig. 1 for the high and low albumin groups. The mean "a" value of each group of patients in the table fixes the vertical- or y-axis intercept of the straight line, while the mean "b" value represents its slope. A study of Fig. 1 reveals that the high albumin patients demonstrated a much better antibody response both in the rate of development and in actual concentration than the patients of the low albumin group. By applying the t-test to the difference in the slopes represented here, it is found that there is a significant differ-

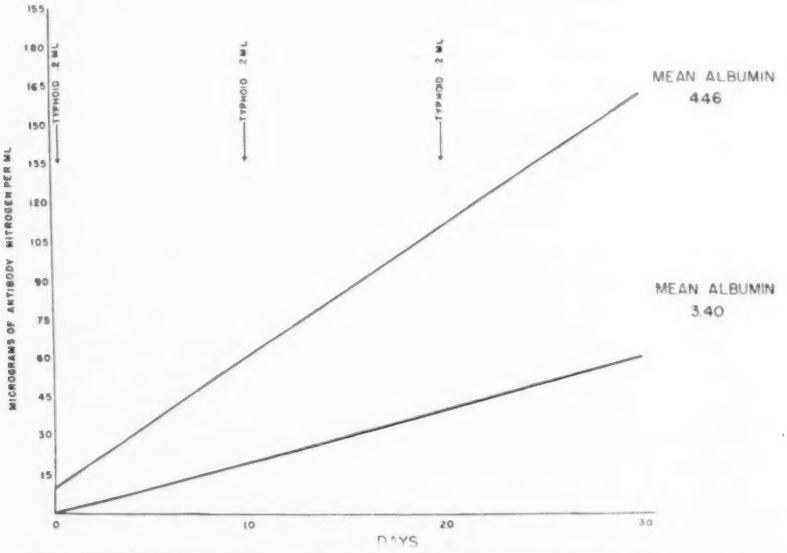

FIG. 1.—Antibody response with time for the high and low albumin groups.

ence in antibody responses when comparing the 2 groups (Table 2). In making this analysis the assumption was made that the antibody response follows a straight line relationship with time. Since it seems likely that this assumption is an approximating one and not exactly true, as a check on the analytic method the t-test was also applied to differences in antibody levels for the 2 groups at successive time intervals. The difference in antibody response for the high and low albumin groups first becomes significant (P less than .01) at 10 days. Thus, there seems to be a good positive correlation between serum albumin level and antibody response in these patients, and the approximating assumption of the method of least squares is supported.

As a level for redividing the patients into 2 sets with respect to the value of the individual's mean total globulin, 3.00 gm. per 100 ml. of serum was used. This value was approximately the average total globulin value for the diabetic population at present under study. The high globulin group of 14 patients, with a group mean globulin value of 4.22 gm. per 100 ml. gave a better antibody response than the low globulin group of 11 patients whose mean globulin value for the group was 2.71 gm. per 100 ml. However, the difference in antibody response between these 2 groups was found not to be of statistical sig-

TABLE 1.—INDIVIDUAL PATIENT DATA

	Individual Mean Serum—			*Individual Typhoid Antibody Responses*							*Calculated Constants*	
				Serum antibody-nitrogen in mcg/ml. at the indicated intervals in days								
Patient	*Albumin gm./100 ml.*	*Total Globulin gm./100 ml.*	*Gamma Globulin gm./100 ml.*	*0*	*5*	*10*	*15*	*20*	*25*	*30*	*y-axis intercept "a"*	*Slope of straight line "b"*
1. Rb	5.36	2.0	1.38	3	15	23	31	31	—	—	2.23	1.66
2. Lw	4.84	3.0	1.38	3	0	0	3	19	11	7	0.36	0.38
3. Pi	4.64	3.1	1.61	0	7	39	79	111	127	147	−8.84	5.37
4. Ba	4.51	3.4	1.74	3	67	131	171	155	187	176	41.64	5.62
5. Ru	4.48	2.6	1.47	0	19	27	—	67	—	—	−0.30	3.26
6. Go	4.48	2.8	1.59	13	45	59	59	71	79	63	26.86	1.79
7. Gi	4.47	3.1	1.64	7	19	87	111	147	164	191	5.89	6.43
8. Cu	4.47	2.1	1.16	11	17	31	79	85	134	115	−2.02	4.62
9. Hi	4.41	2.5	1.29	3	11	15	114	143	159	139	−17.91	6.14
10. De	4.26	3.3	1.78	0	67	115	153	131	143	179	35.74	5.05
11. Ul	4.25	3.1	1.10	27	23	163	191	211	219	251	34.50	7.92
12. Ia	4.04	2.8	1.50	2	22	42	62	102	—	—	−0.25	4.19
13. Al	4.00	3.7	1.56	7	79	151	203	235	—	—	16.58	11.61
14. Ho	3.99	4.0	2.06	0	3	1	9	15	—	—	−1.74	0.72
15. Mu	3.98	2.7	1.30	11	3	15	39	59	71	95	−4.85	3.07
16. Fa	3.81	3.9	2.60	0	0	15	43	67	—	—	−10.90	3.52
17. Ol	3.56	3.1	1.88	0	0	7	11	3	19	27	−2.90	0.82
18. Pe	3.54	3.2	1.45	19	23	27	83	100	152	174	−4.77	5.70
19. Pa	3.52	4.0	2.49	0	5	11	11	23	47	59	−7.38	1.95
20. Fe	3.27	2.3	1.13	1	15	23	35	43	—	—	1.76	2.13
21. Sh	3.25	3.2	1.60	3	0	0	7	0	—	—	1.69	0.03
22. Sc	3.20	2.8	1.32	0	3	11	23	35	—	—	−3.86	1.79
23. Ca	3.12	3.0	1.92	0	0	7	11	3	19	27	−2.90	0.82
24. Ha	2.57	3.3	2.01	3	39	59	75	91	103	115	15.28	3.55
25. Bn	2.15	3.1	0.87	0	11	35	31	27	19	23	8.26	0.73

The serum antibody-nitrogen values have been corrected for non-specific sediment by subtracting an average sediment blank value from each antibody determination in place of the usual and more accurate method of determining a blank for each serum sample. The constants, "*a*" and "*b*", in the 2 columns at the right represent the constants of the straight line equation, $y = a + bx$, where y is the time in days and x is the antibody concentration. These values were calculated by the method of least squares.

nificance probably, as shown by the data listed in Table 2 for these 2 groups.

Somewhat similar results were obtained when the attribute used for the correlation study was the serum gamma-globulin. An arbitrary value of 1.50 gm. per 100 ml. for the gamma-globulin level for grouping purposes was employed, with the result that 13 patients had mean values above this level (group mean value 1.88 gm. per 100 ml.) and 12 diabetics had gamma-globulin mean values equal to or below this value (group mean value 1.28 gm. per 100 ml.). A statistical analysis of the differences in antibody responses between the 2 gamma-globulin groups of patients indicated that the observed differences were probably due to chance and that no significant correlation existed between antibody concentration and serum gamma-globulin concentration in these patients (Table 2).

Attempts were also made to correlate the hemoglobin concentration with the antibody response in these patients but without success.

In order to characterize further those diabetics who demonstrated good immune responses, the various attributes described above were combined 2 at a time for grouping purposes, using the same critical levels of the protein fractions for separating the patients into high or low groups. Employing both albumin and total globulin, 4 groups of patients resulted: Group 1, high albumin-high globulin; Group 2, high albumin-low globulin; Group 3, low albumin-high globulin; Group 4, low albumin-low globulin. The mean antibody responses for each of these groups are shown plotted against time in Fig. 2 with each line labeled with the proper group designation. These plots are based on the data presented in the lower segment of Table 2. The high

TABLE 2—DATA FOR GROUPS OF PATIENTS

Group Designation	*No. of Cases*	*Group Range of Serum Fraction gm./100 ml.*	*Mean Antibody Response Data for Groups*				
			Mean "a" Value	*Mean "b" Value*	*Mean-slope Standard Deviation*	*t-value of difference in slopes*	*Probability or P-value*
High Albumin	13	4.00 or greater	10.30	4.93	2.92	2.98	less than 0.01
Low Albumin	12	3.99 or less	−1.00	2.07	1.64		
High Total Globulin	14	3.1 or greater	8.72	4.22	3.27	1.39	0.2
Low Total Globulin	11	3.0 or less	−0.08	2.71	1.74		
High Gamma Globulin	13	1.51 or greater	8.39	3.64	3.22	0.15	0.9
Low Gamma Globulin	12	1.50 or less	1.09	3.47	2.31		
1. High Alb. & High T. Glob.	6	as above	20.92	7.00	2.48		
2. High Alb. & Low T. Glob.	7	as above	1.28	3.15	2.00	1 & 2 3.10	0.01
3. Low Alb. & High T. Glob.	8	as above	0.94	2.13	1.96	1 & 3 4.13	0.001
4. Low Alb. & Low T. Glob.	4	as above	2.46	1.95	0.93	1 & 4 3.83	0.01

The 25 cases listed in Table 1 are here thrown into high and low groups using the 3 serum protein fractions successively as the attribute to be correlated with the antibody response, in the upper part of the table. In the lower part of the table the albumin and total globulin fractions are combined as attributes for a similar study. In the latter part of the table the t-values and the probability values are given only for the differences in slopes between the 1st group and each of the remaining 3 groups. See the legend of Table 1 for an explanation of the various constants.

albumin-high globulin group is significantly different from all the other groups, but the differences in antibody concentrations between any 2 of the 3 lower groups as determined from the slopes of the lines is not significant. It should be noted here that the magnitudes of the line-slopes shown in Fig. 2 decrease in the order in which the groups are listed.

Thus, the diabetics exhibiting the best antibody responses are those persons whose albumin and total globulin concentrations approach the higher values found in these patients. The mean slope of the high albumin group as plotted in Fig. 1 was found to have a value of 4.93 while the mean slope of the high albumin-high globulin group of Fig. 2 has a value of 7.00. Thus, those patients characterized by belonging to the latter group had a much better antibody response than the patients in the former and more inclusive group.

Four similar groupings were made of these patients by utilizing the albumin and gamma globulin combinations. Although the plots of the mean antibody responses resembled those recorded in Fig. 2, differences between group responses were not significant and in addition the plots of the low albumin-high gamma globulin and low albumin-low gamma globulin groups were reversed in position or in magnitude of the slope from that expected, in contrast to the groupings presented in Fig. 2.

Discussion. The data and the analyses presented indicate that our diabetic patients can be characterized as to their immune response to typhoid vaccine by examining the serum albumin level or better yet by examining both the albumin and total globulin. This is not meant to imply that there is a direct connection between albumin formation and antibody synthesis in the body. This idea would be contrary to existing information which indicates that the liver cells produce albumin[10,12] while

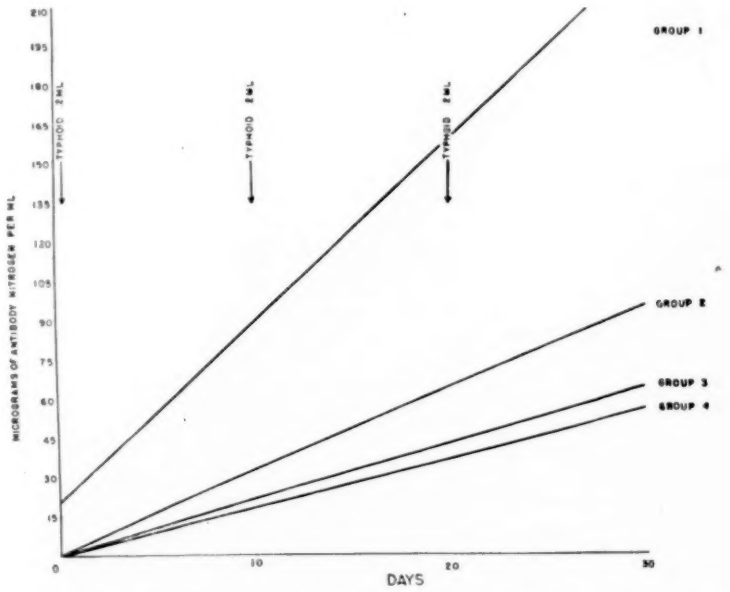

FIG. 2.—Antibody response with time for 4 groups of patients based on albumin and total globulin levels.

other cells probably produce antibody globulin[2,5]. However, there may be some rather indirect connection between these factors which bring about the correlations observed.

Others have found that a marked rise in immune antibody is associated with a simultaneous increase of the globulin fraction of the serum[1,3]. The diabetic patients here examined did not show this effect, probably because the immunizing stimulus was made relatively small in order to mimic more nearly the chronic, localized infections often observed associated with diabetes, and in order not to place too great a challenge on the antibody-producing ability of these persons. Hyperimmunization might induce all of these subjects to reach approximately the same height of antibody response and hence defeat the purpose of the study.

Although statistical analysis has indicated significance of the data presented, since the size of the group of the patients is small, further observations will be necessary to ascertain that the recorded correlations apply to diabetics in general whose physical condition approximates that of our patients.

Summary. Twenty-five hospitalized diabetic patients were studied for their antibody responses to typhoid immunization. With the small doses of vaccine used there was found a good positive correlation between the antibody response and serum albumin concentration. Those patients with both high albumin and high total globulin concentrations according to the arbitrary classification employed demonstrated the best antibody response, although the number of patients in this group was quite small. The antibody response reflected both the rate of antibody production and the ultimate level attained over the experimental period. No correlation could be found under the conditions used between the total globulin alone, the gamma-globulin, or the hemoglobin and the antibody response.

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THE COEXISTENCE OF CIRRHOSIS OF THE LIVER AND GLOMERULONEPHRITIS

Report of 14 Cases

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THE present report describes the occurrence of glomerulonephritis in 14 cases of cirrhosis of the liver. These occurred in 200 consecutive patients with cirrhosis of the liver observed in the Goldwater Memorial Hospital (Columbia Division) from 1936 to 1949, and hence represent an incidence of 7%. Eight other cirrhotics with hematuria and albuminuria were excluded from the study because evidence for an unequivocal diagnosis of glomerulonephritis was inadequate. Sixty of the cases came to autopsy of which 7 (11.7%) were reported to have glomerulonephritis. The higher incidence of renal disease in the autopsied series suggests that the 2 diseases may coexist more frequently than is apparent clinically. The uniform character of the renal lesion and the time relation between the development of nephritis and cirrhosis suggest that the association may be more than casual.

The diagnosis of cirrhosis was established by biopsy or autopsy in 13 of the 14 cases. Ten were classified as Laennec's cirrhosis, 3 as post-necrotic cirrhosis and 1 as a "mixed" type. There were 10 males and 4 females ranging in age from 24 to 63 years with an average age of 43.6 years.

Upon admission to the hospital 12 patients showed signs of advanced hepatic failure, and 2 had only moderate changes. The latter patients (Cases 3 and 6) subsequently showed signs of advanced failure. The duration of hepatic failure preceding entry varied from 3 months to 3 years. The clinical findings obtained during the period of study are listed in Table 1 and reveal the classical signs of the disease. Ascites, edema, jaundice, hepatomegaly, splenomegaly, and vascular spiders were seen in the large majority of the patients. Hemorrhagic phenomena, such as epistaxis, gingival bleeding, and purpura were noted in 8 cases. However, jaundice and hemorrhagic tendencies usually were slight in degree. Laboratory changes were also characteristic of hepatic cirrhosis. In Table 2 are listed 2 sets of laboratory data for each case. The 1st set of data represents values obtained upon admission. The 2nd set is selected to indicate the clinical sequences: 1) values

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TABLE 1.—PHYSICAL SIGNS IN 14 PATIENTS WITH CIRRHOSIS AND NEPHRITIS

Case	Age	Sex	Antecedent Factors	Duration of Failure Before Entry	Ascites	Edema	Jaundice	Spiders	Palp. Liver	Palp. Spleen	Esoph. Varices	Bleeding Tendency	Merc. Diuretics	Period of Observation (years)	Biopsy	Autopsy
1	45	M	alcoholism	4 mos.	+	+	+	+	+	+	?	+	+	5	+	
2	57	M	"	3 mos.	+	+	+	+	+	+	+	0	+	2	0	0
3	43	F	"	6 mos.	+	+	+	+	+	+	0	0	0	5	0	+
4	41	M	"	4 mos.	+	+	+	+	+	+	0	-	+	4	+	
5	24	M	"	6 mos.	+	+	+	+	+	+	?	+	+	2	0	+
6	46	M	"	6 mos.	+	+	+	+	+	+	?	+	0	7	+	
7	62	M	"	12 mos.	+	+	+	+	+	+	?	+	+	5/12	0	+
8	36	F	alc. & viral hepatitis	4 mos.	+	+	+	+	+	+	0	+	0	2	0	+
9	34	M	viral hepatitis	12 mos.	+	+	+	0	+	0	+	0	0	1/12	0	+
10	25	F	" "	latent 12 yrs.	+	+	+	+	+	0	0	+	0	2	0	+
11	58	F	hyperthyroid	12 mos.	+	+	0	0	+	0	?	0	+	2	+	+
12	63	M	alcoholism	3 yrs.	+	+	+	0	+	+	+	0	0	12	+	0
13	31	M	"	2 yrs.	+	+	+	0	+	+	+	+	+	5	+	
14	46	M	"	16 mos.	+	+	0	+	+	+	0	0	0	1	+	

TABLE 2.—LABORATORY FINDINGS IN 14 CIRRHOTICS WITH NEPHRITIS

Case	S. Proteins Gm./100 cc.		S. Cholesterol Mg./100 cc.		Ceph. Flocc.	BSP at 30 min.	Ser. Bilirub. Mg./100 cc.	Alk. Phosphatase	NPN /100 cc.	Urinalysis				Conc. Test	Urea Clear. Test %	P.S.P. at 2 hrs.	ASL Titer	Throat Cult. Hemolytic Strept.
	Alb.	Glob.	Total	Ester						RBC	WBC	Casts	Alb.					
1. Entry 1943	3.7	3.4	208	—	3+	68	2.0	3	28	0	0	0	±	1.029	139	100	166	—
Nephritis 1946	2.9	2.9	206	139	2+	42	1.0	5.5	123	4+	+	4+	4+	1.014	26	40	1600	pos.
2. Entry Jan. 1938	2.8	4.5	172	—	3+	40	tr.	—	30	0	0	0	0	1.021	—	65	82	—
Nephritis Mar. 1938	2.1	3.2	246	—	3+	36	tr.	—	64	4+	2+	+	4+	1.015	—	45	333	neg.
3. Entry 1941	4.1	2.2	285	119	1+	20	2.5	17	17	0	0	0	0	1.020	—	—	—	neg.
Nephritis 1946	3.7	2.7	—	—	3+	—	10	—	35	0	0	2+	2+	—	—	—	200	—
4. Entry 1946	2.3	4.2	180	103	4+	63	1.5	10	32	0	0	0	0	1.027	100	90	—	—
Nephritis 1949	1.6	4.7	122	41	4+	42	10.5	17	55	4+	+	+	2+	1.010	59	30	625	pos.
5. Entry 1947	4.4	2.5	138	88	4+	15	1.0	11	35	0	0	0	+	1.030	—	70	250	neg.
Nephritis 1948	2.8	2.2	121	76	4+	20	2.8	—	130	2+	2+	2+	2+	1.012	—	50	—	neg.
6. Entry 1940	4.1	3.6	211	—	±	12	tr.	—	24	0	0	0	0	1.027	125	—	—	—
Nephritis 1947	2.7	3.6	110	—	+	9	0.8	—	64	4+	+	+	2+	1.012	30	34	333	neg.
7. Entry 1948	3.0	4.3	143	93	4+	41	2.0	13	23	±	±	0	±	1.020	—	44	—	—
Terminal 1949	1.8	3.7	125	32	4+	57	28.0	13	68	0	±	0	±	1.010	—	—	—	—
8. Entry (Nephritis) 1942	2.6	4.5	179	67	4+	40	2.7	4	29	3+	0	0	+	1.024	134	80	620	—
Terminal 1944	2.0	3.7	290	—	3+	80	2.0	—	96	3+	3+	+	4+	1.021	—	—	62	—
9. Entry (Nephritis) 4/1944	1.5	3.3	165	—	3+	25	tr.	8	60	3+	3+	+	3+	1.014	—	70	—	neg.
Terminal June 1944	2.3	3.6	—	—	3+	44	13.0	—	41	4+	3+	+	4+	1.016	51	—	1000	—
10. Entry (Nephritis) 1939	2.7	2.9	400	—	0	44	2.0	7	30	2+	+	±	2+	1.030	65	80	71	neg.
Terminal 1942	1.4	3.3	194	90	3+	65	10.0	8.5	77	3+	0	+	2+	1.018	90	60	333	neg.
11. Entry (Nephritis) 1943	3.5	2.7	300	—	2+	40	tr.	18	16	+	2+	±	3+	1.023	70	50	—	—
Terminal 1944	3.3	3.5	333	—	3+	60	tr.	—	50	+	2+	0	3+	1.020	—	—	—	—
12. Entry (Nephritis) 1938	2.7	4.7	208	134	2+	40	tr.	6	25	+	+	+	4+	1.023	85	80	625	pos.
Follow-up 1946	3.3	3.2	200	—	2+	60	tr.	—	34	+	+	+	4+	1.018	65	50	144	—
13. Entry (Nephritis) 1940	2.3	3.5	112	76	0	28	tr.	—	69	4+	2+	+	3+	1.015	36	40	100	neg.
Follow-up 1945	4.5	2.5	160	—	0	20	2.0	—	30	+	0	0	±	1.024	100	75	1666	neg.
14. Entry (Nephritis) 1945	3.0	4.5	225	146	4+	24	tr.	18	41	4+	+	+	2+	1.012	44	75	833	neg.
Follow-up 1946	4.3	3.2	298	211	4+	10	tr.	—	42	0	0	0	0	1.017	75	65	333	neg.

TABLE 3.—DATA PERTINENT TO NEPHRITIS IN 14 CIRRHOTICS

Case	Antecedent Factors	Onset Present at entry Post Cirrhosis	Signs: Facial Edema	Signs: Fundi	B.P. Peak Values	Type Nephritis	Course of Diseases: Cirrhosis	Course of Diseases: Nephritis	Remarks
1.	Tonsillitis	3 yrs.	+	0	180/90	chr.	impr.	station.	Liver fail. 1943. Good response to ther. Onset nephr. 1946. Chr. course 3 yrs. +
2.	U. R. I.	5 mos.	+	0	220/130	ac.	impr.	recov.	Liver fail. 1937. Good response to ther. Acute neph. 1938. Recovery after 5 mos. Hematemesis and death 1940. No aut.
3.	U. R. I.	4 yrs.	+	0	90/40	ac.	fail.	fail.	Liver fail. 1941. Benign course 5 yrs. Sudden onset cholemia 1946. Death in 2 wks. Aut.: Laennec's cirrhosis, ac. glomerulonephr. (unsuspected).
4.	Tonsillitis	2 yrs.	+	0	130/80	ac.	imp.	recov.	Liver fail. 1946. Good response to ther. Acute nephr. 1948. Recur. 1949. Apparent recov. after 6 mos.
5.	Thrombophlebitis of legs	at entry	+	0	135/70	chr.	fail.	fail.	Thrombophleb. legs 10 yrs. No albuminuria. Ascites 1946. Alb. 1947. Death 1948. Aut.: mixed cirrhosis; mult. thromboses; chr. glomerulonephr.
6.	Cellulitisof legs	6 yrs.	0	0	140/80	ac.	impr.	recov.	Minimal cirrh. 1940. Liver fail. 1943. Good response to ther. Ac. nephr. 1946; recov. in 1 yr.
7.	Unknown	at entry	0	0	210/106	chr.	fail.	fail.	Progr. liver fail. 18 mos. Aut.: Laennec's cirrh.; prim. ca. liver; chr. glomerulonephr. (unsuspected).
8.	Unknown	at entry	+	0	170/110	subac.	impr.	fail.	Liver fail. at entry (1942). Hematuria and alb. without impaired func. Benign course 2 yrs. Sudden renal fail. and death 1944. Aut.: Post-necrotic cirrh.; subac. glomerulonephr.
9.	Unknown	at entry	0	0	115/65	subac.	fail.	fail.	Hepatitis 1 yr. bef. entry. Urine neg. until 2 mo. bef. entry. Rapid fail. coma and death in 1 mo. Aut.: Post-necrotic cirrh.; subac. glomerulonephr.
10.	U. R. I.	at entry	+	4+	170/110	chr.	fail.	fail.	Ac. viral hepatitis 1930. Symptom-free until nephr. 1937; 3 exacerbations of nephr. with progr. hep. fail. Aut.: Post-necrotic cirrh., chr. glomerulonephr.
11.	Unknown	at entry	+	0	230/90	chr.	fail.	fail.	Nephr. and cirrh. noted 1 yr. bef. entry. Progr. fail. and death. Aut.: Laennec's cirrh.; chr. glomerulonephr.
12.	Tonsillitis	at entry	+	+	190/100	chr.	impr.	station.	Nephr. and cirrh. at entry. Benign course 12 yrs. Sudden death. Prob. coron. thromb. No aut.
13.	Thrombophlebitis of legs	at entry	0	0	180/90	subac.	recov.	recov.	Hematemesis, ascites, normal ur. 1941. Nephr. at entry 1943. Recov. from both dis. 57 abdom. taps.
14.	U. R. I.	at entry	+	0	180/110	ac	impr.	recov.	Liver fail. 16 mos. Signs of nephr. 2 mos. before entry. One exacerbation of nephr. in hospital. Recov. from both diseases.

obtained at the peak of nephritis in those who developed the disease subsequent to entry; 2) terminal values in those who entered with nephritis and died of the disease; 3) follow-up values in those who entered with nephritis but later showed improvement.

Certain clinical features related to the development of nephritis are shown in Table 3. It is difficult to assess the relative importance of the 2 disease processes in these patients. However, it is our impression that intercurrent nephritis precipitated hepatic failure in most instances. For example, in 4 patients (Cases 8, 10, 13, 14) the presence of hepatic disease was either latent or unrecognized until intercurrent nephritis caused the development of edema and ascites. Five others (Cases 1, 2, 3, 4, 6) who had made considerable recovery from hepatic failure, suffered relapses at the onset of nephritis, characterized by a sharp

decrease in serum albumin and abrupt reappearance of ascites and edema. Since hypoalbuminemia, ascites, and edema may be present both in cirrhosis of the liver and in the nephrotic phase of glomerulonephritis it was not possible to ascribe these signs to either disease alone. In 6 instances the appearance of jaundice during the nephritis suggested that both diseases were active (Cases 2, 3, 4, 5, 9, 10).

The onset of acute nephritis and the exacerbation of chronic nephritis appeared to be related to upper respiratory and throat infections in 7 cases. In 3 others there was a suggestive relation of the nephritis to thrombophlebitis of the legs, and in 4 instances there was no known antecedent infection. In 3 of the latter 4 cases, the onset of nephritis was poorly documented and a precipitating infection might well have escaped attention.

In 5 cases, nephritis was acute or subacute with subsequent healing; in 5 cases it followed a chronic course with characteristic exacerbations and remissions; in 4 others the nephritis pursued a steadily progressive, fatal course. Facial edema was observed in 10 cases, hypertension in 9, azotemia in 10, albuminuria and hematuria in 12 cases. Tests of renal function, such as phenolsulphonephthalein excretion, urea clearance, and concentration tests were impaired in most cases, but these changes were often not manifest until a late stage of the nephritis (Table 2). In the presence of hepatic damage alone it is not unusual to find somewhat increased P.S.P. excretion, due presumably to the fact that the liver normally excretes some of the dye (estimated at about 15%). It is possible that the values are higher in this series of cases than might be expected in nephritis unassociated with liver damage. Throat cultures taken on 11 cases showed positive growth for hemolytic streptococcus in only 3. Since this may be a transitory finding in nephritis, this result is not unusual. However, antistreptolysin titers were elevated in 10 of the 12 cases so studied.

The time relationship between the onset of cirrhosis and nephritis was of particular interest. In 10 well-documented cases, cirrhosis preceded the onset of nephritis by months or years. Five of these developed nephritis while under observation, and in 5 other cases adequate data were obtained from previous hospital admissions to establish this fact. In the remaining 4 instances (Cases 7, 8, 11, 12) the times of onset could not be established. In no case did nephritis precede the onset of cirrhosis, as best one could determine by history or signs.

Figures 1, 2, and 3 illustrate the different clinical forms of nephritis encountered by these 14 patients.

The chief pathologic findings in the 7 autopsied cases were classified as follows: Laennec's cirrhosis, 3; postnecrotic cirrhosis, 3; nodular cirrhosis associated with multiple thromboses, 1; chr. glomerulonephritis, 4; subacute, 2; acute, 1. In each instance glomerulonephritis was of the intercapillary type.* The severity and extent of the renal changes bore no apparent relation to the degree of hepatic damage.

Discussion. The association of hepatic and renal changes has long been noted in the medical literature. In certain

* Intercapillary glomerulonephritis[13] differs from the extracapillary type in that proliferation of the capsule with the formation of crescents and adhesions between the glomerulus and capsule is either absent or extremely rare. The lesion in the intercapillary type is diffuse, spreading peripherally from the hilum. In the extracapillary type the lesion is focal and initiated at the periphery. In the early stages of the intercapillary type there is a leukocytic inflammatory reaction. Subsequently there is hyalinization of the glomerular capillary walls and the connective tissue as well as splitting of the basement membrane. The connective tissue of Bowman's capsule but not its epithelium undergoes proliferation.

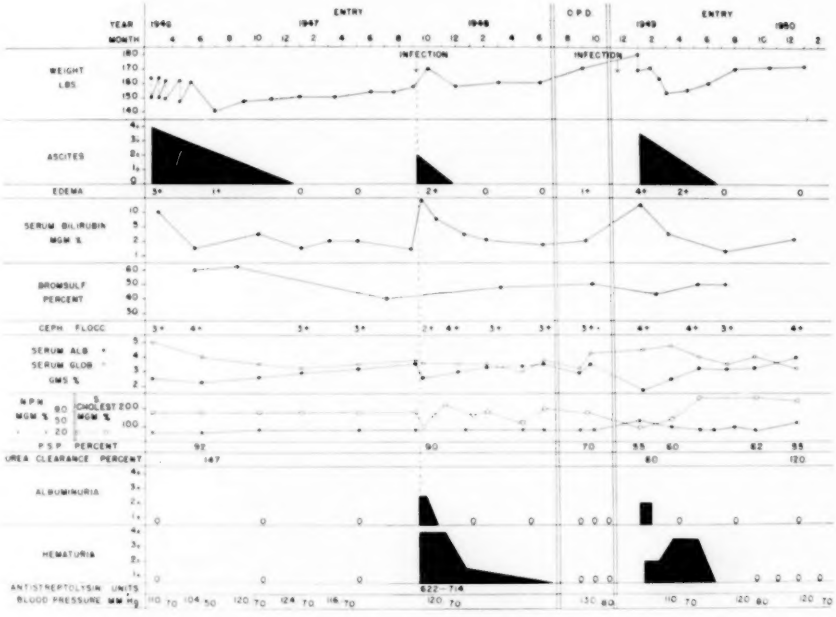

FIG. 1. CASE 4.—Chart of case of Laennec's cirrhosis with 2 bouts of acute glomerulonephritis with subsequent healing. The case is similar to Cases 2,6,13,14.

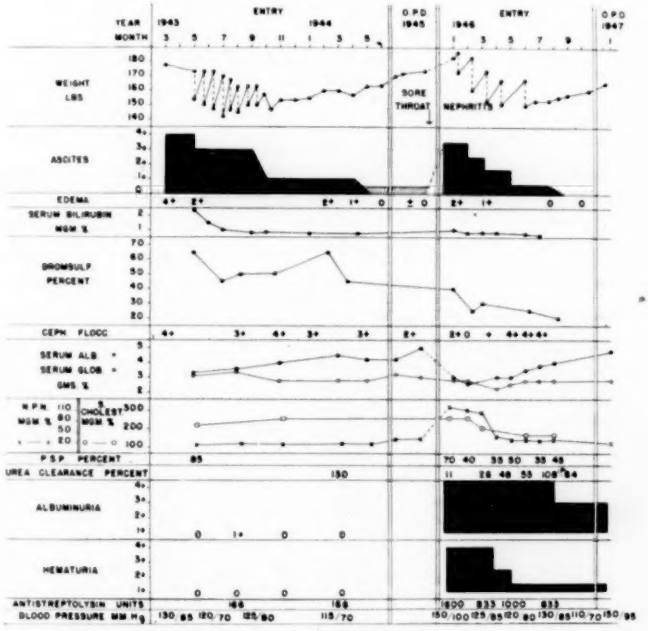

FIG. 2. CASE 1.—Chart of case of Laennec's cirrhosis with intercurrent glomerulonephritis which became chronic. The case is similar to Case 10.

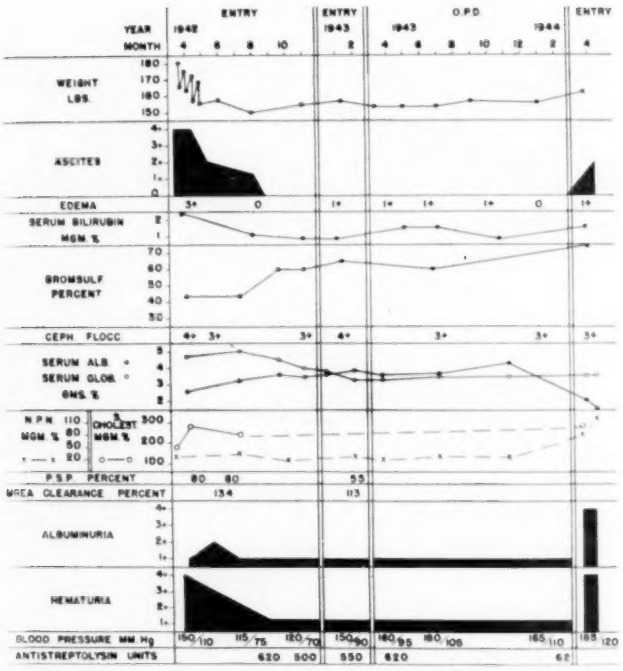

FIG. 3. CASE 8.—Chart of case of both cirrhosis and glomerulonephritis at entry. Renal failure was the apparent cause of death (autopsy). Similar to Cases 3,5,9, and 11.

diseases and intoxications the 2 organs are involved[10]. In the pathologic physiology of shock, interplay between hepatic and renal hormonal factors has been described[15]. In so-called "hepatorenal syndrome", occurring in patients who have suffered from shock during surgery on or near the biliary tract and in prolonged obstructive jaundice degenerative changes are found chiefly in the renal tubules[5,9,16]. Similar tubular changes are found in patients dying of acute yellow atrophy[12]. Since no significant glomerular abnormalities have been described in these conditions, there would seem to be little relation between them and the problem under discussion.

In experimental choline deficiency, Griffith and Wade[6] and others[3,7,8] have described the occurrence of hemorrhagic cortical necrosis in young rats. In the acute stage these lesions are primarily tubular. As late sequellae, however, secondary glomerular changes and renal arteriolar degeneration take place. These are characterized by thickening of Bowman's capsule, hypertrophy and hyalinization of the renal arterioles. Chaikoff and his associates[2] have described the production of glomerular changes in 3 of 12 dogs fed high-protein diets and alcohol. The renal changes were characterized by scattered fibrosis and hyalinization of glomeruli, capsular adhesions, cortical hemorrhages, and tubular degeneration. In a recent report, Baxter and Ashworth[1] described renal changes in 25 cases of human cirrhosis studied post mortem. Cases that were complicated by renal disease of "inflammatory nature" were excluded from the series. In the large majority there was granular and hydropic swelling of the tubules. Scattered hyalinized glomeruli were found in 19 cases, of which 10 showed periglomerular fibrosis. In most

of these altered glomeruli there was thickening of the basement membrane, and arterial or arteriolar sclerosis. "Because of this association it seems likely that periglomerular fibrosis and hyaline thickening of the glomerular basement membrane were due to arterial and arteriolar sclerosis, thus resembling the ischemic changes in the glomeruli described by Kimmelstiel."

The above findings appear to bear little analogy or relation to the present group of cases. In 6 patients nephritis developed while they were being fed diets rich in choline and protein. In 8 others nephritis developed before dietary therapy was instituted. The lesion of intercapillary glomerulonephritis, so constant in this series, is distinct from that described by Baxter and Ashworth. Mercurial diuretics, although frequently employed in the group, are not known to produce this glomerular lesion. Moreover, 7 patients developed the disease at a time when they were not receiving mercurials.

In this series of 14 patients the onset of acute nephritis or the exacerbation of chronic nephritis appeared to be a sequel to infection, just as in other cases of glomerulonephritis uncomplicated by hepatic disease[14]. In 10 instances upper respiratory infections, throat infections, or thrombophlebitis preceded the onset of the disease by a few weeks. In 10 of 12 cases studied there was a sharp rise of antistreptolysin titer, suggesting recent invasion of the hemolytic streptococcus[4]. Although only 3 cases had positive throat cultures for the organism, this is not unusual, since only 4 patients were observed at the time of this initiating infection.

The incidence of glomerulonephritis in general hospital populations is said to be about 0.5 to 1.0% of medical admissions. In the present series the incidence is well in excess of these figures. If the inference is correct, namely that cirrhosis of the liver predisposes to the development of glomerulonephritis, it may help shed some light on the pathogenesis of the latter disease.

Summary and Conclusions. 1. In a series of 200 cases of cirrhosis of the liver, coexisting glomerulonephritis was observed in 14 (7%). Sixty of the cases came to autopsy of which 7 (11.7%) showed both cirrhosis of the liver and glomerulonephritis. This incidence seems to be beyond a normal expectancy.

2. The nephritis assumed diverse clinical patterns, namely acute, subacute, and chronic. In 10 of 14 cases there was evidence of hemolytic streptococcal infection preceding the onset of acute nephritis or the exacerbation of chronic nephritis. In all 7 autopsied cases the nephritis was of the intercapillary type.

3. In all well documented cases cirrhosis of the liver preceded the onset of nephritis.

4. The basis for this relationship (if it exists) is not evident.

Case Reports. Case 1. S. B., a 42-year-old Irish-born janitor, entered on 4/29/43 because of abdominal swelling. He was treated with quinine for malaria 24 years previously. For 20 years he had drunk excessively of whiskey and wine. However, his diet was said to be adequate. About 4 months prior to entry he noted edema of the legs and for 3 months, progressive abdominal swelling. For 1 month there were anorexia and intermittent abdominal pains. On admission he appeared emaciated and ill. The breath had an "amine" odor. Sclerae were icteric and the skin showed greyish-brown pigmentation. Dilated venules and vascular spiders were seen on the face, arms, and thorax. The abdomen was huge and the legs were swollen. The tongue was red and smooth. Breathing was shallow. The heart sounds were normal. The blood pressure was 132/85. After abdominal paracentesis a firm liver edge was felt 8 cm. below the ribs in the right nipple line, and the spleen tip was felt in the left axilla at the costal margin.

The patient was placed at bed rest and fed a nutritious diet rich in protein, supplemented with brewer's yeast, thiamin chloride and nicotinic acid. He also received mercurial diuretics and choline chloride. Over a period

of 14 months he made steady improvement as shown by the loss of ascites and edema, gain in body weight and strength. Tests of liver function showed improvement.

After discharge in July, 1944, he was seen periodically in the clinic. Although he resumed his drinking habits his diet was good and he was in fair health until December, 1945, when he had a severe sore throat, tender cervical nodes, fever and chills. The patient was treated with sulfadiazine and the throat symptoms abated. However, 2 weeks later signs of acute nephritis appeared. Shortly thereafter he entered the hospital because of massive ascites and edema.

On admission the findings were similar to those of the first entry. In addition he showed signs of acute nephritis, namely periorbital edema, hypertension, nitrogen retention, albuminuria, hematuria, granular casts, diminished renal function, and elevated antistreptolysin titer. Repeated cultures of the nose and throat were negative for hemolytic streptococcus. The serum albumin had decreased from 5.2 to 2.3 gm. %. Liver function, as reflected by the bromsulfalein dye test, serum bilirubin, cephalin flocculation reaction was not further impaired. After 5 abdominal paracenteses the ascites and edema disappeared and the serum albumin increased. Gross hematuria and azotemia subsided, but albuminuria and microscopic hematuria persisted.

In the past 3 years (1947-1949) the patient resumed his drinking habits but claims to be eating well. The liver and spleen are palpably enlarged as before, but he has been free of ascites, edema, and jaundice. The blood pressure has become elevated (150/95) and the urine shows albuminuria 3+ and microscopic hematuria.

Case 4. V. O'D., a 41-year-old American born laborer, entered Bellevue Hospital in March, 1946, because of jaundice and ascites. There was a story of arsenical therapy 12 years ago and of alcoholism and malnutrition for 10 years. For about 4 months there was progressive weakness, anorexia, swelling of the abdomen and legs, jaundice and paresthesias. Examination showed a drowsy, weak, malnourished man. The sclerae and skin were icteric and the breath was foul. There were several vascular spiders on the face and neck, and dilated veins over the abdomen. Ascites and peripheral edema were pronounced. The tongue was bright red and smooth and the teeth were carious. The heart and lungs were normal. The liver edge was felt 5 cm. below the ribs and the spleen was at the costal rim. There was a small umbilical hernia. Additional findings included gynecomastia, scanty body hair, atrophic testes, clubbed fingers and toes, palmar erythema, and signs of polyneuritis. Laboratory tests indicated hepatic failure.

The patient was placed at bed rest, fed a nutritious diet, and injected with mercurial diuretics. Five paracenteses were performed in 13 months, after which he was transferred to Goldwater Memorial Hospital. Ascites disappeared in 2 months and he made steady, but slow improvement. After 15 months his course had reached a plateau. At this time (Sept., 1947) trial was made of intravenous liver extract. By mishap he received a contaminated preparation which caused a severe pyrogenic reaction, associated with a prompt return of jaundice, ascites and edema together with a fall in serum albumin, hematuria and albuminuria. With antibiotic therapy the symptoms subsided. Albuminuria disappeared in 3 weeks. However, hematuria persisted for about 6 months. He was discharged in June, 1948, two years after entry. The patient remained in fair health and carried on moderate activity until January, 1949, when he became acutely ill with pharyngitis, cellulitis of the leg, chills and fever. Throat culture was positive for *Staph. aureus*, coagulase positive. On entry there was plain evidence of hepatic and renal failure, as shown by the presence of jaundice, ascites, facial edema, anasarca, albuminuria, hematuria and granular casts. The blood pressure was 110/70 and the nonprotein nitrogen 55 mg.

After penicillin therapy he became afebrile in 1 week. With bed rest, nutritious diet, and supportive care he made improvement. Jaundice, ascites and edema subsided. The serum albumin rose steadily from 1.6 to 4.1 gm. %. Albuminuria disappeared in 2 weeks, but hematuria persisted for 5 months. He feels well and is ambulatory. However, there is still marked impairment of liver functions.

In brief, this patient appears to have had 2 bouts of acute glomerulonephritis with recovery. Such cases, although unusual, have been reported[11].

Case 8. I. J., a 36-year-old American-born housewife, entered because of jaundice and abdominal swelling. There was a family history of hypertension. In childhood she had scarlet fever and diphtheria. Her diet always had been meager in dairy foods and meat. Twenty years ago she had mild hyperthyroidism treated with iodides. For 10 years she had imbibed excessively of wine and whiskey. Her gums had bled with slight trauma for many years.

For 6 months there was progressive anorexia and loss of weight, and for 5 months, amenorrhea. Two months before entry marked the onset of abdominal swelling, jaundice, flatulence, and drowsiness. Examination on admission showed an obese, drowsy, dyspneic woman with flushed face. Several vascular

spiders were seen on the face and body, and there was a fine tremor of the hands. Sclerae were icteric. Fundi were normal. Teeth were carious and the gums boggy. The tongue was beefy red and the lips fissured. The thyroid was of normal size and had no bruit. Blood pressure was 150/100, pulse 110, and temperature 100°. The heart was slightly enlarged to the left and the lungs were normal. The abdomen was distended with fluid. After paracentesis a firm, non-tender liver edge was felt 10 cm. below the ribs and the spleen 4 cm. below the costal border. Rectal, vaginal, and neurological examinations were normal. There was 3+ edema of the legs.

Laboratory tests showed impaired hepatic function, albuminuria and microscopic hematuria. In addition to values recorded in Table 1, there were decreased values for serum vitamin A and carotenoids, prothrombin time 33 sec. (normal 18 to 24) B. M. R. +5, and erythrocyte sedimentation rate 95 mm. per hour.

During the first month in the hospital there was constant fever (100 to 101°) and tachycardia. After 4 abdominal paracenteses she lost 25 lbs. in weight. Intravenous pyelograms showed poor filling of the calyces but retrograde pyelograms showed no abnormal shadows. The urea clearance and P. S. P. tests were normal.

On a nutritious, high-protein diet supplemented with brewer's yeast, thiamin, nicotinamide, ascorbic acid, and alpha-tocopherol she made steady improvement as shown by disappearance of jaundice, fever, ascites, edema, and vascular spiders. Tests of liver function showed improvement. She became mentally alert. Normal menses returned. The liver and spleen remained palpable, albuminuria and hematuria persisted, although less pronounced than on entry. The blood pressure declined from an initial value of 150/110 to 120/70.

Two months later she returned to the hospital because of an abscessed tooth, which was extracted without mishap. Tests of renal and hepatic function showed no significant changes. She was seen at intervals in the clinic during the next year, during which she felt well. The blood pressure remained elevated throughout this period. About 14 months after discharge from the hospital, and without apparent cause, she noted headaches, anorexia, nausea, vomiting, diarrhea, and abdominal swelling. On examination she was weak and lethargic. There were periorbital edema and gross tremors of the hand. The sclerae were icteric and the fundi normal. The tongue was coated and the pharynx injected. The lungs and heart showed no changes. The blood pressure was 145/110, temperature 99°, pulse 80. The abdomen was moderately distended with fluid. The liver and spleen were felt 7 cm. and 4 cm. respectively below the ribs. Extremities showed 2+ edema and coarse tremors. There was an inconstant Babinski sign.

In the course of 5 days there was rapid deterioration, characterized by fever, weakness, tremors, and stupor. In this short period the blood pressure rose to 185/125 and the nonprotein nitrogen increased from 30 to 96 mg. Urinalysis showed increased hematuria and albuminuria. The CO_2 combining power was 45 vols. % and the blood sugar 145 mg. Because of hectic fever (reaching 106°) and leukocytosis, septicemia was suspected, but blood cultures were sterile. On the 7th day the patient lapsed into coma and died.

Autopsy: (chief findings): subacute intercapillary glomerulonephritis; post-necrotic cirrhosis; esophageal varices; splenomegaly; acute bronchitis (*Staph. albus*); phlegmonous gastroenteritis; chronic thyroiditis.

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LOCALIZED PAROXYSMAL HYPERHIDROSIS

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The mechanisms of sweating are incompletely understood. Textbooks of pharmacology and physiology describe perspiration solely as a cholinergic phenomenon[1,3]; yet it is well known to the clinician that epinephrine, directly or indirectly, can sometimes cause profuse diaphoresis[2]. Recently Wada demonstrated that epinephrine intracutaneously causes sweating that is not inhibited by atropine[8]. At about the time Wada's paper was published, a patient with paroxysms of localized hyperhidrosis came to our attention and provided an opportunity to explore the sweating mechanism.

Case Report. R. K., a 41 year old instrument engineer, male, had noticed that a small area on the right wrist would become drenched with sweat when he became excited or tense. He had first noticed this strange occurrence about a year after recovery from measles (rubeola) 24 years prior to these studies. Eight years ago a duodenal ulcer had necessitated a subtotal gastric resection. Upon resumption of normal eating the patient was entirely relieved of his ulcer symptoms but was mildly troubled by a "dumping" syndrome, that is, a feeling of generalized weakness and palpitation shortly after the ingestion of liquids, particularly sweetened beverages or milk. Curiously, the "dumping" symptoms were accompanied by the same localized sweating habitually caused by emotional tension. Neither the hyperhidrosis nor the "dumping" syndrome was sufficiently annoying to interfere with the patient's normal life, and he did not seek medical attention. He was studied as a cooperative volunteer. Physical examination and a detailed neurologic examination revealed nothing remarkable. There was neither evidence of, nor history to suggest, trauma to any portion of the right arm or wrist.

Experiments. In all the following observations, sweating was demonstrated by means of the starch-iodine reaction as described by Wada[8]. Each test with bathenecol and epinephrine was repeated 4 times.

In 8 tests it was obvious that an area about 3 in. in diameter around the distal end of the right ulna became covered with large beads of perspiration within 3 minutes after the ingestion of a glass (8 oz.) of milk. Sweating elsewhere, visualized by the same technique, was not comparable in amount and was in no way unusual. The feeling of weakness and palpitation always appeared simultaneously with the sweating. After an ordinary solid meal, no "dumping" symptoms were produced but there was excessive sweating upon the right wrist in 40 to 60 min. This sweating was less than that which appeared with the "dumping" symptoms. Since the "dumping" produced such a predictable trigger mechanism, no attempt was made to confirm the patient's thoroughly credible statement that the hyperhidrosis was also caused by emotional tension. In exploring the possible causes for the hyperhidrosis, the following tests were performed:

1. Five mg. of bathenechol chloride (Urecholine chloride, urethane of B-Methyl-choline chloride) were injected subcutaneously. This drug is a parasympathomimetic, more lasting in its effect than acetylcholine. Ten to 15 minutes later the patient developed a drenching, generalized sweat, followed

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by a mild chill and an urgent desire to defecate and urinate. There was no excessive perspiration on the right wrist and no more on the right than on the left.

2. Bathenechol chloride (2½ parts diluted in 10^3, 10^4, 10^5, and 10^6 parts of saline). On separate occasions 0.10 cc. of each mixture was injected intracutaneously into corresponding areas of each wrist. All but the highest dilution caused sweating of equal intensity on both sides, and the highest dilution caused no sweating on either wrist. With the lower dilutions, sweating was roughly proportional to the dose.

3. Epinephrine (1 part diluted in 10^6, 10^7, 10^8, and 10^9 parts of saline). On separate occasions 0.10 cc. of each mixture was injected intracutaneously into corresponding areas of each wrist. Again sweating was produced equally on the 2 sides approximately in proportion to the dose; the highest dilution caused no sweating on either wrist.

4. A histamine wheal, produced in the manner described by Lewis[5], was of the normal "triple response" type on both wrists.

5. Atropine sulfate (1 part diluted in 10^7 parts of saline). One tenth cc. of this mixture was injected intracutaneously into the right wrist. The "dumping" reaction was then produced in the usual manner with milk. The area around the injection stood out as an island of almost no sweating in the midst of the customary hyperhidrosis.

6. Sodium phenobarbital (4 grains injected intramuscularly). An hour later the patient became sleepy, and at that time was given twice the amount of milk ordinarily used to produce the "dumping" reaction. Within 3 minutes he had the usual symptoms, but even after 8 minutes no sweating appeared upon the wrist. Another 8 ounces of milk were ingested, aggravating the "dumping" symptoms, and 3 minutes later the characteristic pattern of hyperhidrosis was produced, but at no time did the quantity of sweat approximate the amount seen in each of the previous "dumping" experiments. While the patient was still somnolent, 0.10 cc. of bathenechol chloride $1:10^4$ was injected intracutaneously. Sweating was produced in the same degree as it had been by this drug previously, indicating a failure of the phenobarbital to alter the excitability of the sweat glands themselves.

Discussion and Conclusions. From these observations the following conclusions seem warranted: 1. The patient's paroxysms of hyperhidrosis were not the result of a localized sensitivity to either of the 2 substances known to produce sweating (acetylcholine and epinephrine). Wada's observations on the sudorific action of epinephrine[8] are confirmed in this patient, as they were in 10 other individuals tested by us. Similarly, the patient's response to bathenecol was substantially the same as that observed by us in 10 healthly men. Clearly, in no dilution was there a difference between the wrists in the sweat-response to either Urecholine or epinephrine, nor was there a difference in the threshold response to either drug.

2. The negative neurologic examination, the absence of trauma, the long history, and the normal histamine response are also consistent with the interpretation that the localized sweating was not due to any abnormality in the skin itself. Such abnormalities have been suggested under different circumstances in other cases of localized hyperhidrosis[6], but in this case seem unlikely.

3. The hyperhidrosis, although not caused by a localized sensitivity to acetylcholine, seems nevertheless to

have been mediated by this substance, since it was almost completely blocked by atropine.

4. Another possibility seems to be the presence of some localized area in the central nervous system, possibly in the hypothalamus, which, when activated by certain stimuli ("dumping" reaction, strong emotion) produced a reflex hyperhidrosis in one small area of skin. This hypothesis is supported by the marked mitigation of the reaction by sodium phenobarbital, a drug which does not significantly alter the peripheral sweat mechanisms. It is interesting that the stimuli which produced localized hyperhidrosis in this patient will, when marked, produce generalized sweating in many individuals. One might visualize a central area in which normal reflex arcs are facilitated or in some way augmented. The situation may represent a minor, localized form of the peculiar syndrome in which paroxysmal generalized hyperhidrosis occurs, sometimes with sufficient severity to lower the body temperature several degrees[4]. An example of the latter condition was observed by us in a young physician whose mother also suffered from the same disorder. This individual's response to intracutaneous epinephrine and bathenecol approximated the findings in our patient. Another physician is known who developed episodes of sweating confined to one half of his body following a febrile illness which could possibly have been encephalitis[7]. The present patient had measles not long before he first noticed the hyperhidrosis; it may be that measles encephalitis was the primary cause.

Summary. 1. A patient with paroxysmal hyperhidrosis of the right wrist is described. The attacks occurred with emotional tension and with the post-gastrectomy "dumping" syndrome.

2. Studies are described which tend to rule out a local cause in the skin of the wrist and which suggest that the hyperhidrosis is caused by a localized area of hyper-excitability in the central nervous system.

3. The direct sudorific action of epinephrine was confirmed.

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COCCIDIOMYCOCIS: A REVIEW

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COCCIDIOIDOMYCOSIS or Coccidiomycosis (this term is more easily pronounced) is an infectious disease caused by the fungus *Coccidioides immitis* (Rixford and Gilchrist), the spores of which generally enter the body through the respiratory tract. An acute, benign, self-limited, influenza-like primary disease often referred to as "San Joaquin Valley fever", "Valley fever", "Desert fever" or "Desert Rheumatism" is frequent in certain regions of the United States and perhaps in Argentina. A secondary, progressive, granulomatous, often lethal infection, called coccidial granuloma is rare, and generally occurs a short time after the initial infection. Exogenous reinfection seems to be unusual.

History. In 1892, Wernicke[268] and Posadas[192,193] in Argentina observed in a skin lesion a protozoan-like organism. A similar case in the USA was reported by Rixford[211] and Gilchrist[212] 2 years later. The fungus was first cultured by Ophuls, Moffitt and Ash[186] in 1900. Up to 1914 only 24 cases of coccidial granuloma were on record[161]. The whole subject remained dormant until 1936 to 1938 when J. Smith[218a], Gifford[99-102], and Dickson[73-76a] presented evidence that "Valley Fever" known for a long time in the California San Joaquin Valley, was caused by the *C. immitis*.

Important etiologic confirmation came from the case of a medical student, who 9 days after handling a Coccidioides culture in Dickson's laboratory developed typical symptoms of "Valley fever"[76]. During World War II the establishment of large training centers in the western states afforded a great opportunity for investigation of the disease by epidemiologists[230].

[233,227], pathologists[98], and clinicians[104, 105]. A complete account of the knowledge thus accumulated will be presented in this paper.

Mycology. The fungus *C. immitis* has both a tissue sporogenic (or parasitic) phase and a culture mycelial (or saprophytic) phase. Synonyms and the botanic classification have been enumerated by Baker, Mrak and Smith[11]. In the human and animal body spherules measuring 10 to 80 microns and even larger (up to 262 micron, Schenken[221]) may be found. They contain a few to several hundred spherical or globose or irregular endospores (2 to 10 microns in diameter). With rupture of the spherule the endospores may be expelled and be seen free in the tissue. The free endospores are difficult to distinguish from body and ordinary yeast cells and a diagnosis may, therefore, not be substantiated on the finding of free lying endospores alone.

Spherules develop from fragments of the mycelium (arthrospores) which evidently enter with dust through the upper respiratory tract. Wolbach[273] gave a comprehensive description of the fate of injected mycelia in the rabbit and the formation of projections from spherules incubated in slide cultures was described by MacNeal[161]. In cultures the development of branching septate mycelia from spherules is easily demonstrated. Prickles and club like excrescences measuring 2 to 5 microns have been observed projecting from spherules in tissue[3,11,116,17]. However, Smith[228] does not believe that budding of spherules in animal tissues[71] ever occurs in this organism.

On the other hand, culture spherules are only occasionally formed[150]. MacNeal[161] observed multiplication of spherules in pus mixed with ascitic fluid or horse serum containing sterile kidney slices. This observation has been confirmed by some investigators[51,52] but not by others[253]. The former report in addition evidence of conjugation prior to sporulation; the existence of this phenomenon has been accepted by Negroni[181] but not confirmed by Baker[9]. In Baker's[9] experience only certain strains were capable of producing spherules in artificial media. Schlumberger[222], however, easily produced spherules in citrated blood or serum at 37.5 C. from mycelial culture growth in slowly revolving tubes in a roller apparatus designed for tissue culture. Spherules could not be obtained by this method using brain heart infusion as a medium. The "culture spherules" were smaller (10 to 20 microns) than tissue spherules. Spherules have been considered by several authors to be asci[77,161,178,184, 248,259] but more recent workers have believed them to be sporangia[11,51,228].

Growth of the fungus in tissue occurs by means of the endospores, which after liberation from the spherules redevelop in the tissues into mature (endospore-containing) spherules. The endospores are formed by cleavage. Occasionally, a spherule instead of containing numerous small endospores may show only a few, large ones (up to 40 microns). The walls of such large endospores are usually thick and similar to that of a normal spherule. The mature spherule generally has a wall 2 microns in thickness. Some giant spherules[221] are described as having capsules which measure 21 microns in thickness!

Cultures can be easily grown on all common laboratory media, growing especially well on Sabourand's glucose agar, blood agar, Smith's selective medium[227], Stewart's medium[249], or Wilhelm's[269] medium. A cottony white to creamy colony develops. With age the appearance may become powdery and the color range from buff to brown. The culture mount shows hyphae with deeply staining,

rectangular or ellipsoid arthrospores measuring 2 by 5 microns[56]. With further aging the hyphae may fragment and the liberation of arthrospores constitutes an extreme hazard to laboratory workers.

Laboratory Infections. Several laboratory infections have been recorded and there is evidence that dissemination of arthrospores may be very extensive indeed. Infections seem to have occurred in the second and third floors of a building in which C. E. Smith's laboratory occupied the first floor. Tomlinson[263], and Dickson[76a] reported instances of the disease in medical students handling culture material. The incubation period in Dickson's case was 9 days. From similar experience incubation periods up to 2 weeks have been noted. Bush[34] reported infection from a contaminated cotton-wad used in culture work and Looney[158] an instance in a technician who developed the disease after closely inspecting an open Petri dish culture. Another case[189] was observed in a chemist who was wearing a gauze mask while preparing extracts of culture material for skin tests. At Duke University one fatal and several less severe infections occurred in dish-washers in the cleaning room of the Department of Bacteriology[236]. These were thought to be due to spores adherent to the outside of culture tubes. In C. E. Smith's laboratory 21 persons[158] showed positive skin tests probably due to laboratory infections. Most of these had no evidence of symptoms. Similar experience with laboratory workers have been reported[158, 236,270] and it is safe to predict that routine skin testing of workers exposed to Coccidioides cultures would demonstrate even more frequent evidence of subclinical infections. Nevertheless, in spite of the accumulated evidence, D. T. Smith[236] has stated that the handling of cultures of this organism is safe if the loop used has been moistened with water. On the other hand, E. C. Smith discontinued examination of cultures submitted for identification in order to avoid additional laboratory infections. Keeney[140] designed an ingenious protective cabinet in which cultures could be handled with safety.

Laboratory Procedures. The most important single laboratory procedure for the diagnosis of Coccidiomycosis is the demonstration of the causative agent. Direct mounts of pus, sputum, gastric contents, and so on, may be indicative[56] but most observers do not recommend simple microscopy as a reliable procedure[235,251]. The demonstration of typical spherules with endospores in the tissues removed by biopsy may be of conclusive diagnostic value.

The injection of material into guinea pigs (intratesticular) or mice (intraperitoneal) is a widely recommended method. Gastric washings may be treated with cupric sulphate (0.05% final concentration) and after 4 hours centrifuged and examined[56]. The cupric sulphate treatment of material is also indicated for animal injections[227]. Intranasal instillation of infectious material[252] is dangerous for obvious reasons, especially if it is culture material which is used in the inoculum.

Although Smith's selective medium[227] presents relatively scanty growth of Coccidioides, practically no contaminating bacilli or other fungi develop.

Arthrospores appear only about 3 to 5 days after the culture growth has become visible and young cultures (without spores) are not infectious for laboratory animals[148,249]. The fungus has been found to be pathogenic for dogs and rabbits[148], monkeys[192], and hamsters[222]. Frogs, however, developed only small nodularities in the peritoneum 8 days after injection[222]. The intratesticular inoculation of guinea

pigs, a recommended routine procedure[227], produces orchitis after 10 to 30 days.

Etiologically it is important to recognize that the fungus growth is excellent on carrots, potatoes, cactus, strips of wood, and so on. This is especially noteworthy since completely dried out cultures of agar or cactus strips even after 7 years have been shown to grow easily after an addition of glucose broth[247].

Biology of the Fungus. None of the carbohydrates are fermented by *C. immitis*[10,56,119b]. Milk was reported to be coagulated and peptonized[56,119b, 247] but this was not confirmed in Italy[42a,51]. Ciferri[51] observed the digestion of keratin (hair and feathers). Gelatin is liquified[119b]. Magnesium is indispensable for growth of the organism[214] and experiments with Zn, Fe, Cr and Cd were also reported in the same paper. Numerous substances may serve as source of carbon as for instance ammonium lactate[119b], acetic acid (but not formic acid[247]), numerous hexoses, disaccharides, trisaccharides, glucosides, polysaccharides, alcohols, organic and amino acids, amides, and others. The above data elaborated by Baker and Smith[10] resulted from the testing of 15 different strains. Few variations were reported with these different strains except in the utilization of sucrose and lactose. Only a small amount of nitrogen is necessary for the growth of Coccidioides and this can be obtained at a wide range of acidity (pH 2,02-12, 13). Inhibition is reported at pH 1,07 and 14 (Bump[30]). Ammonia is formed especially in acid media[30]. The consumption of glucose by the fungus does not surpress the production and assimilation of ammonia[247]. All ammonium salts especially the chloride[181a] are excellent sources of nitrogen. Urea is also usable but can not be utilized as a source for nitrogen and carbon at the same time in contradistinction to the aminoacids which may be so utilized[247]. Preformed vitamins or similar growth factors are not required for satisfactory growth[214]. No hydrogen sulphide, indole, carbinol are produced nor is nitrate reduced[181b]. The fungus is killed in 4 minutes at 60° C. At 52° C., 95% of the viable cells are destroyed. A temperature of 46° C. does not affect the cells even after 2 hours[214] and under those conditions there was no difference in the growth[214] of the simple mycelial and the sporulating culture. The optimal temperature for growth is 30 C.[181b].

Epidemiology. The transmission of the disease is not completely clear. Spores have been found in the soil[81,249, 234] and in different animals in endemic areas. Emmons[81] suggested that certain wild rodents, especially pocket mice, might be the hosts of the parasite. But, since cattle, sheep, swine and even a gorilla in a zoo showed lesions due to airborne infection, the possibility that the rodents might have been infected from the soil and not have been primarily responsible for the contamination of the soil, cannot be denied.

An impressive instance of the concept of the infection from dust was obtained during an expedition of 14 high school teachers and pupils to the Californian Desert in San Benito County. Ten out of the group were involved in the digging of a hole in the process of hunting a rattlesnake. Two to 3 weeks later all 10 showed positive coccidioidin skin tests. The 4 individuals who did not participate in this dusty maneuver escaped infection. *C. immitis* was later isolated from the vicinity of the same rattlesnake hole[67]. Rare instances of infection through a wound caused by a cactus spine[110] and from an abrasion received during picking walnuts[73] have been reported and there have been suspicions that infec-

tion might occur from fruits and vegetables grown in the endemic areas. Nevertheless, the greatest evidence points in the direction of infection by dust via the air passages. Not only is the incidence higher during summer months[231] and after sandstorms, but infection can be minimized by proper dust control[229]. Rosenthal[216,217] tried to demonstrate the mechanism leading to contamination of the soil and claimed that spherules could be seen in dried sputum mixed with soil for periods up to 240 days. In addition, the formation of occasional mycelia was reported by the same author. However, the culture proof presented in the pertinent papers is not convincing and the reliability of direct microscopy is open to question. Rosenthal[218,219] felt that Coccidioides spherules were infectious since they produced constant lung lesions when introduced into the bronchi in 15 guinea pigs. He indicated the possibility of infection from man to man and animal to man, but this view has not been accepted by other workers in the field[15,17,24a,235]. It is, however, fair to state that since spherules introduced into the bronchial tree, testis or blood stream[62] of animals have produced the disease one should consider similar possibilities in man even if clinical experience to date does not indicate that this is likely[15,24a,235].

Spread from man to man should be kept in mind as a possibility in view of the observation of mycelial forms of Coccidioides developing in pulmonary cavities[98,108], (discussion to [108,235,267]).

Geographic Distribution. Cases of Coccidiomycosis have been observed principally in California, and most of the evidence related to the distribution has been obviously based on surveys by means of the Coccidioidin skin test. The area of highest incidence of infection is the southern San Joaquin Valley[104,224,270,257]. The incidence in the northern part of the valley is sporadic. The San Joaquin Valley is a large basin in Southern California covering an area of 18,000 square miles and a length of 450 miles with a width about 40 miles in average. The soil of the area is sandy and the climate very dry. In certain areas the rain fall is as low as 0 to 10 inches per year.

Outside this endemic area occasional cases have been reported from other parts of California[11,20a,144]. Instances detected by skin testing and occasional cases of active disease have been reported from Texas, in its western half and the Mexican border[227,242,162, 223,36,37,94,112] Southern New Mexico and Southern and central Arizona[6,19,80,81, 152,174,191,251,274] the southern tip of Nevada and southwest Utah are also endemic regions.

Outside North America a few cases have been reported in the Chaco[39,137, 164,181f,192,193,268], which comprises a great part of Paraguay west of the Paraguay river, the adjacent parts of Bolivia and Argentina. The area comprises about 38,000 square miles with a population consisting mostly of nomadic Indians. The rainfall is heavy (63 inches) and the mean annual temperature 73°F. Recently a case of Coccidiomycosis observed in an arid area (Rio Colorado in Argentina)[181d,e] stimulated extensive skin testing among 2650 school children who were 6 to 15 years of age. The incidence was highest in Rio Colorado: ten, 2% positive and five, 4% doubtful results. In an adult group taken mostly from hospitals and consisting of inhabitants of areas south and west of Buenos Aires 25 gave a positive reaction and 12 a doubtful in a total number of 305 tested. It would seem that Argentina very likely is a second important endemic area of Coccidiomycosis.

A case has been recently reported from Venezuela[38] in a native woman, who had lived all her life in that country. The diagnosis was verified by cul-

ture, biopsy and positive skin test and the complement fixation test was made by C. E. Smith. The town from which the patient came is in an arid region. A case supposedly occurring in Nicaragua or Santo Domingo was that of an American Soldier who lived 3 years in these countries. However, there is no statement in the report[271] about the life history of the patient and there appears to be a good likelihood that he contracted the disease in one of the endemic areas in the United States rather than during his stay in Central America.

Three cases have been observed in the vicinity of Naples, Italy[42,207], and cultures from these have been verified by C. E. Smith and others. In spite of some differences in pathogenicity, there is no reason to question the identity of the fungus isolated in Italy[11] or to attempt to subdivide the species[42].

A case reported from China[47] would appear to be anything but Coccidiomycosis, since the yeast like culture mount was clearly not representative of this organism. A case observed in Canada[31] was not verified by cultural studies. A Mexican publication described an organism of 18 microns diameter with double contour[189]. In absence of illustrations this case may be considered to be of doubtful nature. Cases reported from Brazil[159] have been caused by *Blastomyces Brasilensis.*

Diagnostic Skin Test (Coccidioidin). Equivocal skin test results with culture emulsions were first reported[59] in 1913. Davis[70] first successfully produced Coccidioidin in 1924, although Smith[233] gave Cummins[66] historical priority. Definite steps toward the successful production of filtrates were made by Hirsch and others[21,103,118,119,119a,122,126]. Kessel's[144] Coccidioidin was a heat killed broth culture which contained ground mycelia prior to filtration. Stewart[248] in 1940 grew Coccidioides on synthetic media, and filtered it through a 2% collodion filter but triturated the culture prior to filtration. Standardization was attempted on infected, sensitive guinea pigs. Most of the recent work has been done by C. E. Smith[233] who grew the fungus on a medium containing asparagin, dextrose, glycerol and several salts. Four to 10 strains were used as inocula to eliminate possible antigenic deficiencies of one single strain, even if the skin reactions in man[233] and guinea pigs[144] had been equal with different strains. Many lots of Coccidioidin were discarded because of the frequency with which nonspecific reactions occurred[84]. Careful comparison showed that the grinding of the mycelia does not contribute to the quality of the final product and that Asparagin cultures yield a higher antigenic titer than the media used by Stewart[233,248].

Stewart's Coccidioidin[248] contained 0.97 mg. protein nitrogen and 2.92 mg. non protein nitrogen per cc. of undiluted substance. A polysacharide which was produced in synthetic media and gave a skin reaction was demonstrated by Hassid[111]. Galacturonic acid, glucose and an unidentified sugar was reported[111]. After acetylation with loss of nitrogen the substance was not antigenic in the skin test but still active in the precipitin test. Coccidiodin is very heat stable, withstanding autoclaving for 30 minutes at 15 pounds pressure [233,248]. This fact is highly important for practical purposes, since the activity of Coccidioidin is not destroyed by the customary means of sterilization of syringes. One must either use new glassware each time or use syringes exclusively for the Coccidioidin test or the syringe must be soaked over night in dichromate cleaning solution or boiled in this solution[233].

Smith[233] denied the occurrence of sensitization due to skin tests with Coc-

cidioidin in guinea pigs and human volunteers but sensitization of animals by this method has been reported[119]. This question is important, since retesting is frequently necessary. In view of the extensive experience of Smith[233] his statements are generally accepted. He denied also the appearance of complement fixing or precipitating antibodies after skin tests. The strength of skin test solution recommended by Smith[233] is 1:1000 to 1: 10,000 for cases of erythema nodosum; 1:100 for mass surveys. About 10% of positive reactors would be missed with the 1:1000 dilution. In the case of individuals with disseminated disease 1:10 or even undiluted Coccidioidin may be used.

Undiluted antigen and antigen diluted even to 1:100 are stable, when refrigerated, for years and do not show reduction of potency. However, bacterial contamination may falsify results completely. Much care should be given to the preparation of the glassware, sterile diluents and refrigeration, since discrepancies in reactions observed by Smith[232] cannot be explained save as the result of contamination of the solution. (Patients tested elsewhere and reported as negative, showed positive reactions when retested by Smith. Naturally, the possibility of infection in the interval between the 2 skin tests had to be excluded[232].)

Patients with erythema nodosum are extremely sensitive to Coccidioidin, and the absence of a skin reaction in such cases practically rules out infection with Coccidioides immitis. Erythema nodosum and multiforme were precipitated on several occasions by strongly positive reaction to skin tests[144,233].

The skin sensitivity is reported to persist for as long as 10 years[233] although variations in strength of the reaction are known. However, Cheney[43] reported loss of skin sensitivity within 6 months and his observation certainly requires corroboration.

The Coccidioidin test becomes positive in man from 10 to 45 days after exposure[233,257] or 2 to 21 days after onset of the acute disease[233].

In animals, the skin test becomes positive 6 to 7 days after inoculation[16a]. Smith observed failure to react to coccidioidin during the 1st week of illness in one-sixth of patients, but in the 3rd week only 1% of patients without disseminated disease failed to react. The most significant value of Coccidioidin in diagnosis is the observation of "change-overs". The abrupt change from a negative test to a positive reaction with a 1:1000 dilution is considered diagnostic of a recent infection with the fungus. This may be seen as soon as 2 to 21 days after onset of the acute disease[233].

Unfortunately, about 70% of cases with disseminated Coccidiomycosis fail to react even with 1:100 dilution of Coccidioidin. 1:10 dilution or undiluted antigen[126] have been used in such patients but the more concentrated the antigen the higher the incidence of nonspecific cross reaction[121]. In an Ohio orphanage only 1% of the inmates was found to react to Coccidioidin diluted 1:1000, but 50% reacted to a 1:10 dilution. (Furcolow, personal comm. to Smith[233]; similar experience: Aronson *et al*[6].) No acceptable explanation could be found for the positive reactions in the Ohio Valley where Coccidioides is not known to occur in endemic form.

Cross reactions have been observed with *Haplosporangium parvum*[81], a fungus isolated from wild rodents, but the pathogenicity of this organism for man is not known. Smith[232] even considers the possibility of some unknown fungus, the antigenic properties of which could explain the frequency of cross reactions.

Such cross reactions occur also with Blastomycin and Histoplasmin. Persons who have reacted negative to Coccidioidin may exhibit a positive reaction after having a positive Histoplasmin test. The stronger the Histoplasmin reaction, the more frequent and the more intense were the reactions to Coccidioidin. In similar manner persons previously negative to Histoplasmin have been shown to react positively after sensitivity to Coccidioidin has been elicited[232]. Similar results have been seen with Blastomycin[232]. Nevertheless Coccidioidin is considered to be more specific than Histoplasmin if used with a "battery" of several skin testing agents at their appropriate critical titers and if the technical precautions for correct injections and reading of the reaction are observed[232].

Butt[35] compared the accuracy of skin testing with findings at autopsy in persons who died of causes other than Coccidiomycosis. He was able to demonstrate spherules in a limited number of lungs. Coccidioides immitis was recovered from calcified lung foci[62,226].

Coccidioidin has also been used as an antigen in complement fixation and precipitin tests. The complement fixation test may never become positive with mild infections, but following dissemination the varying titer of the test may aid in prognosis. A falling titer indicates improvement and vice-versa. Titers around 250 are not unusual in the progressive disease. With pulmonary cavitations, however, a low titer is the usual finding[235].

Precipitins may develop earlier than complement fixing antibodies and be present even in primary severe localized Coccidiomycosis. They also disappear sooner from the blood than do the complement fixing antibodies. Since the skin test is negative in about 70% of the disseminated cases, the following scheme can be drawn:

	Skin Test	*Precipitin Test*	*Complement Fixation*
Acute benign infection	+	− or +	−
Acute severe but focal and not disseminated disease	+	+	− or +
Disseminating infection	(70%)	±	+

Obviously in the presence of a positive skin reaction a serologic test should be ordered only if severe symptoms exist or dissemination is considered a possibility. On the other hand, the absence of a positive skin reaction when coccidial dissemination is suspected should not preclude the performance of the serologic tests[233]. Antibodies have been demonstrated in blood, pleural and spinal fluid.

Other Laboratory Tests. Elevated red cell sedimentation rate has been reported by practically all observers. This is less pronounced during the primary disease than in the presence of the disseminated granuloma. With pulmonary cavitation a normal sedimentation rate was seen in 72% of cases[235]. A falling rate is generally a good prognostic indication.

Leukocytosis up to 26,000 and more is a frequent occurrence and the differential count often shows an eosinophilia[105]. Such extreme eosinophil values as 89%[270] are unusual but 10 to 29% are reported in the series of Sweigert[257] in 23% of the patients. With the subsiding disease relative and absolute lymphocytosis may develop. This has been used as an indication of an arrested lesion[228].

In the spinal fluid in cases of meningitis there is a pleocytosis (50 to 2000 cells) with lymphocytes predominating (up to 93%)[222] and a disproportionate eosinophilia may be present[1].

The gold curve is inconstantly of the paretic type[222]. False positive Kahn tests[98,254] and Wassermann reactions[53] have been observed during acute Coccidiomycosis.

Spontaneous Coccidiomycosis in Ani-

mals. The disease occurs in a variety of animals indigenous to the Southwestern United States. It has been found in cattle, wild rodents, dogs, swine, sheep and a mountain gorilla in the San Diego Zoo.

More than 600 cases in cattle have been observed since the first report in 1918[103]. Beck's cases[20,21] had either localized lesions resembling tuberculosis in the upper respiratory tract or mediastinal lymph node involvement. Coccidioidin testing has been reported[22]. In Colorado[251] infection was observed in cattle but no complete life history of the animal was available. Also a steer raised in Arizona or New Mexico[252] was found to be infected. From the vicinity of Bakersfield, California[47] additional instances are on record[68]. Formerly it was believed that the disease was limited to older cattle but Coccidioides has been found[69] in 8 to 10 months old calves. In young cattle raised in California or Texas, Bengston[22] has made such findings. Evidence of another endemic area around Phoenix, Arizona, has been offered recently[191]. In a 10 month period 511 cases of Coccidiomycosis were observed, 503 in adult cattle and 8 in calves. All lesions were restricted to the thoracic cage, generally a lymphadenitis. Only 12 cases are reported with pulmonary lesions[191]. Antemortem diagnosis apparently could be made by serologic screen tests[191]. Only those animals which were placed in feedlots contracted the infection. Those originating from range country and destined for immediate slaughter escaped infection with Coccidioides. From one feedlot 25% of 1 herd presented lesions of Coccidiomycosis. No lesions were found in sheep or hogs from this region.

Three infections were reported in dogs[90a,201,238]. Two of these had lived in endemic areas (Arizona and Texas). The third was an English setter which had spent his 2 years of life in Quebec, Canada. Mated with a setter brought from California it became ill shortly thereafter and died a month later in an accident. The lungs and central nervous system were involved by coccidial granuloma. No cultural studies were carried out[201,194].

Unusual was the case of Coccidiomycosis in the mountain gorilla, kept in the San Diego Zoo[168]. Dyspnea and intermittent hemorrhage from the nares were observed after about 40 days of illness and the animal died on the 45th day. Spherules and granulomatous lesions were present in the lungs, spleen, liver and lymph nodes. The source of infection could conceivably be the oat hay used as bedding. This was grown in the vicinity of San Diego and frequently contained lumps of soil.

C. immitis has been cultured from the soil[67,81,249] and from wild rodents in endemic areas[7,80,81,83]. Emmons suggested that these animals could serve as a reservoir of infection and that a further survey of the disease in rodents could be a means of determining the extent of endemic areas. It seems possible that susceptible animals living in the endemic areas are infected from the soil or perhaps from native vegetations.

Subcutaneous inoculation of cattle with Coccidioides produced an infection limited to the point of inoculation and the regional lymph nodes. Intravenous injection of the fungus in calves produced a fatal infection[103].

A report of Coccidioides in the salivary glands of 2 moles is doubtful since cultural proof is lacking[208].

Pathologic Anatomy. Primary infection occurs with rare exception in the lung. The material collected by Forbus[98] from the Armed Forces Institute of Pathology served as basis for study of recent pulmonary foci. In 50 autopsies[98] the characteristics of the primary

lesion were described as follows: 1) Focal lobular pneumonic consolidation similar to nonspecific bacterial pneumonia (case of 74 days of disease). 2) Extensive focal or confluent lobular gelatinous consolidation. These lesions were grossly characterized by the wetness of the tissue and sometimes by its hemorrhagic character. Microscopically fibrin and polymorphonuclear leukocytes predominate. Spherules are very numerous. The outstanding feature is necrosis and this affects the intra-alveolar exudate and surrounding pulmonary structure. The resemblance to tuberculous lesions with early caseation is striking. 3) After only 31 days of disease there was observed[98] in 1 case an ulcerative bronchitis and bronchiectatic dilatation. The lesions showed a large number of spherules and polymorphonuclear leukocytes in the bronchial mucosa. 4) Focal lobular granulomatous consolidation with epithelioid cells and large mononuclear giant cells. Among the granulomatous lesions were small collections of purulent exudate. Forbus[98] did not believe that *restitutio ad integrum* was likely and anticipated fibrous or calcified scars as residua of the lesions.

In the early disease of either the primary or disseminated variety the lymph nodes were large, succulent and even necrotic[98,113]. Hematogenous dissemination to the lung from extrapulmonary foci is not associated with a similar lymph node response. Perforation of the bronchus due to regional necrotizing lymph nodes has been observed[98].

In his 50 cases Forbus[98] found the frequency of organ involvement as follows: lungs, lymph nodes, spleen, skin, liver, kidneys, bones, meninges, adrenal, myocardium, brain, pericardium and pancreas.

Pleural involvement accompanied lung lesions just as in tuberculosis. This is either in form of circumscribed fibrinous plaques, fibrino-purulent or productive granulomatous pleuritis. A large amount of fluid was uncommon in the pleural cavities[55,257] and the inflammation was both localized and diffuse[37].

Peritonitis[220] was rare and pericarditis uncommon[98,152,182a]. The spleen was frequently involved in the disseminated disease. However, the average weight of the spleen in 27 cases[98]was only 200 gm. with the range between 78 and 700 gm. Miliary nodules were the rule but large partially or completely necrotic granulomatous lesions also occurred[98].

Abscess formation was seen but no calcification was ever observed[98].

Calcification was uncommon in lung lesions, and Forbus[98] did not support the view[6] that calcified lesions in Tuberculin-negative individuals were due to Coccidioides infection. Nevertheless spherules have been found occasionally in pulmonary scars[62,226] with and without calcification. The liver and the kidney are not uncommonly sites of infection, especially in the form of isolated granulomas and abscess-like foci. Involvement of the renal pelvis or ureters has not been observed[98]. In one instance portal phlebitis was present.

Bone lesions are as a rule multiple and are not uncommon in disseminated Coccidiomycosis. The spine, pelvis, bones of the hands and feet and tissues about the knee and ankle are most frequently involved. In long bones the Roentgen ray has revealed lesions in both metaphyseal and diaphyseal region. In short bones the lesion is generally found in the diaphysis[23]. The process is purely destructive[164]. It is stated that marginal erosions are always accompanied by a soft tissue abscess and that this frequently calcifies in its later stages[23]. Destructive lesions with periosteal new bone formation and changes resembling

those of osteomyelitis have been seen especially in the short bones of the hands and feet. Spina ventosa has been reported[54].

It has been stated that soft tissue lesions do not extend into bone[172], but other observers disagree[23,40,23].

As in all progressive disseminations the colored patients are very much more frequently seen with bone lesions than white ones. Skin tests are frequently negative in the presence of extensive bone involvement. Skull foci are frequent and important because of the possibility of extension of the disease into the meninges[98]. Outward extension of granuloma of bone may produce large subcutaneous abscesses which eventually result in chronic draining sinuses. Psoas abscesses have been observed[98] and muscles in other areas may become secondarily involved by osteo-articular coccidiomycosis[98].

Arthritis which occurs in the primary form of the disease is commonly accompanied by erythema nodosum, but this is complicated neither by effusion nor suppuration[215]. In one large series of cases not a single instance of arthritis was seen[257], although this is in contrast to the experience of Rosenberg[215].

In the granulomatous phase multiple swollen joints are not uncommon and in this later stage fluctuation and eventually cutaneous nodulation may supervene. In a series of 79 cases[215] the incidence of arthritic localization was as follows: ankle 33, knee 21, foot 16, elbow 11, and wrist 10. As in tuberculosis a destruction of the articular surface with swelling of surrounding tissue may be visible[40]. Cartilage which overlays bone lesions is often destroyed[98] and eventually ankylosis may develop[215].

The incidence of meningitis was reviewed in 1936[1] and 37 cases were found. Courville[61] added 5 more; Schlumberger[222] describes 13 which reappear in the series of 18 of Forbus[98]. The exudate is described as remarkably thick and it may encase the brain stem and other structures at the base of the brain[22,63,98]. Such lesions may result in hydrocephalus[1]. Recently 4 cases of meningitis in late pregnancy[225] have been reported and this complication was claimed to be more than coincidental. How frequently meningitis complicates disseminating Coccidiomycosis is seen from the finding of 18 cases in a series of 50[98].

Brain involvement has been reviewed by Craig[63]. He did not think that granulomas in this region were an important source for meningitis. However, in view of the accumulated evidence pointing to the relationship in tuberculosis one wonders whether similar slicing techniques in Coccidiomycosis might bring to light an identical relationship.

A possible case of eye involvement has been reported[154a]. The spinal cord may be the site of granulomatous lesions independently or simultaneously with the brain and meninges.

Adrenal involvement was recorded 16 times in Forbus'[98] series of 50 cases but no adrenal insufficiency was found in any of these. Most of the lesions were miliary in nature and scattered. However, massive involvement has been observed both with unusual enlargement and extensive necrosis of the glands[35,277] (for discussion see Ophüls [184]). Butt's case[36] had symptomatology of Addison's disease.

Myocardial lesions observed by Forbus[98] were of microscopic size and apparently of little importance. Endocarditis seems to be unusual[85]. Pericarditis may be caused by extension from adjacent lymph nodes or result from hematogenous dissemination[98,182a].

Pancreatic involvement has been found[98] and also lesions in the prostate [98,167] and the seminal vesicles[277]. In general, however, the genito-urinary

system with the exception of the kidney and the prostate are rarely attacked. A unique finding of granulomatous lesions due to Coccidioides in a placenta is briefly mentioned by Smale[225]. The implications, if this finding should be more than casual, are obvious.

Skin lesions may be of various forms. Erythema nodosum is common in the primary form of the disease. In the progressive phases, vesicles, wart-like excrescences and ulcerating lesions may appear. On occasion, subcutaneous nodules, which are metastatic in origin and are accompanied by little inflammatory reaction, are found. After rupture sinus tracts may discharge pus for long periods. Most of the skin lesions appear during dissemination, but in rare instances dissemination may result from primary skin infection[187].

The microscopic picture of coccidial granuloma is rather pleomorphic but is sufficiently characteristic to lead to suspicion of a specific granuloma and to stimulate search for the pathognomonic spherules. Forbus[98] stated that a specific tissue reaction accompanied the different developmental stages of the spherule. In his opinion spherules in the intermediate stages of development attracted mononuclear wandering cells. Mature spherules combined the properties of the endospores and the growing spherule. Endospores are stated to attract polymorphonuclear leukocytes as do ruptured spherules. In long standing lesions only a few spherules may be found or the spherules may even be degenerated and ruptured so that the diagnosis must in these instances be based upon other criteria (such as culture, serology, and skin tests). The endospores are rarely identified in tisuse and cannot be utilized as diagnostic evidence. Due to dehydration and other distorting factors during processing of tissues, marked deformity of the spherules may occur and error based on the acceptance of isolated elements simulating spherules is possible.

Clinical Manifestations. Three forms of Coccidiomycosis can be clinically distinguished: 1) Asymptomatic primary infection. 2) Symptomatic primary infection, a) mild influenza-like respiratory disease; b) more severe pneumonia-like disease. 3) Progressive (disseminated disease—coccidial granuloma).

1) The occurrence of asymptomatic infection is attested by the fact that most of the positive skin reactors have no history of clinical disease or recall only vague symptoms of short duration and little significance. At least 60% of positive reactors appear to have unrecognized infections.

2) The influenza-like primary disease is relatively acute with single or combined symptoms as follows: Fatigue and general malaise are fairly constant; pleural pain was found in 75 to 85%[104, 257], fever in one series was recorded in 60%[104] and 100% in another[257]. Nonproductive cough was present in 50%[257] and 88% of cases[104]; cough accompanied with minimal hemoptysis[104] in 28%. Chills were as frequent as 66%. Great weight loss in a rather short period has been a characteristic finding in many histories (up to 30 pounds in a few weeks). Massive pleurisy is not common (3% in 75 cases[55]). Indefinite gastrointestinal disturbances occur but not frequently.

About 5% of all cases, or 20% of the symptomatic, develop erythema nodosum. The skin lesion appears 2 to 20 days[228] (8 to 15 days[73,75]) after the onset of the acute disease and is localized most frequently on the shins, lateral surface of the thighs, on the knees, buttocks, arms, upper part of the chest and scalp[73,75,54,228]. The "bumps" (this is the popular name in the San Joaquin valley) do not fluctuate but may be very tender and painful. After 48 to 72

hours the erythematous spots turn purplish and fade, and after 4 to 5 days only a brownish pigmentation remains. Rarely, repetition occurs spontaneously after 3 to 4 weeks, more often after skin tests with Coccidioidin or after sandstorms[54] when supposedly large amounts of spores are inhaled. Coincident with erythema nodosum, conjunctivitis and arthralgias are frequent[215]. A marked eosinophilia in the peripheral blood is outstanding during this stage. The skin eruption is an important diagnostic aid and frequently provides the first hint to investigate for Coccidiomycosis. The skin sensitivity to Coccidioidin is very prominent during the presence of the erythema. The importance of Coccidiomycosis as cause of erythema nodosum in the San Joaquin Valley is highlighted by Smith's[23] figures: of 453 cases with erythema nodosum 432 had a positive Coccidioidin test, 11 were due to tuberculosis and 10 undetermined. The erythema occurs twice as often in women as in men although Coccidiomycosis is observed 4 times as often in men than in women. Erythema nodosum must be very rare in negroes; Smith[23] did not see a single case in a series of 524 and only 2 cases have been reported[270]. The special items of laboratory, Roentgen-ray and pathological findings are discussed elsewhere.

3) Progressive disease or Coccidial granuloma occurs in about 1 case out of 500 in white patients but much more frequently in the non-white population. The Mexican rate of the progressive disease is given as 3.5 times that of the white group, the negro rate 14 times, and the Filipino rate 180, and the death rate is correspondingly 5, 23 and 192 times that of the white[102]. Similar conclusions are arrived at[230] in a series of 710 white patients yielding only 8 disseminations while 34 non-white persons yielded 4.

Obviously the figures for the non-white population are limited and corrections may be necessary in the future, but a racial factor seems evident.

Coccidial granuloma was indeed the disease known since Wernicke[268] and Posadas[192,193] but the benign primary forms were recognized only after Gifford's[99,102], J. Smith's[218a] and Dickson's[73-76a] efforts.

The symptomatology obviously depends on the localization which is protean. Meningitis is believed to be more frequent in white persons[23]. The dark skinned races show a tendency toward subcutaneous and periarticular abscesses and in general show much similarity to tuberculosis in all its forms. Smith[230] compares the differential diagnosis of the infection with the index of textbooks of internal medicine.

Tuberculosis presents the most frequent differential diagnostic problem. The only striking or consistent difference is the great rarity of intestinal ulceration in Coccidiomycosis[79,98,107]. Also isolated kidney disease seems to be less common than in tuberculosis. Little is known about the involvement of the female genital tract in Coccidiomycosis. In the section on Pathology an account of common and less common localizations is given and the less common symptomatology may be derived from that.

Combination with tuberculosis has been reported[44,123,138,210,235,256].

Roentgen-ray. A rather copious literature refers to Roentgen-ray findings[16, 23,40,41,53,55,72,90,105,133,134,164,188,195,204,215, 235,257,261,270,272a,b]. The first description is by Bowman[25] in 1919: rather significant papers are Carter's[40,41] Jamison's [133,134], and Smith's[235].

Three groups of findings are distinguished in a series of 96 patients[133] all having the disease at least 2 months.

1) *Nodular parenchymal lesions (23 cases).* These are generally in the midlung (12x) less often in the lower lobes

(7x) and least often in the apical and subapical regions.

2) *Cavities even when large with a very thin wall.* In 35 such cases, 11 instances involved the upper lung field, 15 the middle lung, and 9 the lower lung. Smith[235] describes 148 cavities in the upper and 64 in the lower chest. The diameter of the cyst like structures was 1 to 8 centimeters[133]. Infiltration is usually absent in the surrounding pulmonary tissue. The walls of the cavities may be so fluctuant that ballooning due to air trapping was considered. Such cavities may be present for years with little or no discomfort for the patient, may slowly disappear either by collapse (may however reopen!) or by gradual shrinking. Such residual cavities were observed with little or no change over periods up to 5 years[16,24]. An excellent study of cavities is presented by Smith[235].

Lobectomies have been repeatedly reported[98,188,176,108,109] (also Randolph's discussion[109], Brunn's person. commun.[235]). Some have been done without being published[146], both for cavities and rounded granulomata. Regional resection for small lesions[170a] have been made. Lesions may, however, reappear even after lobectomies[108,109,146,176]. Sometimes repeated hemoptysis even in absence of other symptoms may make surgical removal necessary. The proponents of active surgery give as indications for lobectomy the persistence of a cavity, repeated hemoptysis and the possibility of familial infections. More conservative authors feel that the status of patients even with huge cavities is generally excellent, that collapse can be accomplished by more conservative methods[235] and that secondary infections in families of patients have never been demonstrated[15,17,24a,235].

In regard to the aspect of surgical intervention in these cases, it may be pertinent to note that dissemination in a patient with coccidial cavitation is rare; Smith[235] did not see it at all; only a single case is reported[149].

3) The third group of 21 cases in Jamison's paper[133] refers to persistent pneumonitis. The infiltrates vary from more than a third of the lung field to small hilar foci. In the disseminated disease the mediastinal and hilar adenopathy was most impressive and a final miliary spread developed rapidly and became eventually massively confluent. There is universal agreement that the Roentgen ray findings closely simulate tuberculosis, but in contradistinction to the latter, the clinical course even in the presence of extensive lung infiltration is often asymptomatic and the cavities are cyst-like and thin walled.

Treatment. Many substances have been used in the treatment of Coccidiomycosis and enthusiastic reports are scattered through the literature, frequently based on the experience with 1 or 2 cases. These modes of treatment applied to larger series never could be confirmed. Arsphenamine, crystal violet, gentian violet, thymol, antimony, potassium tartrate, sulfonamides, and iodine have been tried but no evidence of definite benefit has been presented[237a]. Histamine[135], colloidal copper[128], penicillin[4,171], aureomycin[200a], streptomycin[227], either are reported as not improving the patients condition or, as in the case of vaccine therapy, appeared effective only in the hand of the author[127].

Of the actually known antibiotics, Streptothricin inhibits the growth of *C. immitis* in concentration of 30 units per cc. media[214]; plumbagin is fungostatic in a dilution of 1:50.000[220b], as is bacillomycin in the concentration of 0.005 mg. per cc. of media[150a]. Streptomycin does not inhibit the fungus[214] and penicillin seems rather to stimulate than to inhibit the fungus[93a]. General measures and bed rest seem so

far to be as efficient as any "specific" treatment, except surgery[200] in the superficial skin lesions or localized bone granuloma.

As dissemination is rare in white patients, the beneficial effect of treatment can be evaluated only in a large series of proven cases with the controls which are so necessary for a valid evaluation of the benefits of a given treatment.

Summary. The fungus *C. immitis* produces a disease, which is endemic in parts of California and nearby areas and possibly in Argentina. Rare isolated cases in Italy, Venezuela, and a few other places have little epidemiologic importance. The disease seems to be transmitted by air, soil and dust, but no clinical evidence for infection from man to man exists, even if the finding of the highly contagious mycelia in lung cavities indicates such possibility. The Coccidioidin test is fairly specific if used in proper dilution and in combination with at least 2 other fungus antigens. The duration of the skin sensitivity seems to be similar to experiences with tuberculin. The skin test is frequently negative in disseminating disease, but complement fixation and precipitin test may become positive in this condition. Cattle and other animals, especially wild rodents, have spontaneous Coccidiomycosis in the endemic areas. In pathology, anatomy and in the clinic, the disease closely resembles tuberculosis, even though differences in organ localization and Roentgen ray findings as well as discrepancies between extension of cavities and status of the patient exist. No specific treatment is available at this time.

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ADDENDUM:

Several papers have appeared since this manuscript was submitted for publication and in order to bring the review up to date the references are added under the following headings.

Biology of the fungus: **Artagaveytia-Allende, R. C.:** Mycopathologia, **4,** 375, 1949.

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UNDER THE CHARGE OF

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PRESENT STATUS OF ACTH AND CORTISONE THERAPY FROM THE PSYCHIATRIC VIEWPOINT

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AT the present time there appears to be no satisfactory evidence that the use of either ACTH or Cortisone is effective in the treatment of the psychiatric disorders. As with every new drug, there is an initial phase of over-enthusiasm, which has been particularly exemplified with these two hormones, because very early it was shown that they produced an amelioration in a great many varied disorders. Unfortunately, this was not the case in psychiatric diseases. To be sure, no great number of psychiatric patients have received ACTH or Cortisone therapy; however, those that did, have failed to show any change for the better. These hormones have been tried in manic depressive psychosis, schizophrenia, reactive depression, and a variety of psycho-neurotic and neurological illness.

The failure of these hormones to be of aid in the specific therapy of psychiatric disorders in no way detracts from their usefulness as a means of increasing our knowledge of the psychiatric diseases, particularly schizophrenia and manic depressive psychosis. Although ACTH and Cortisone will probably not prove of value in the treatment of so-called "functional" mental disorders, the associated studies may prove fruitful in uncovering many of the heretofore unknown and sometimes unrecognized organic components of these illnesses. Indeed, recent work has indicated this to be the case. We wish to point out the psychiatric aspects of ACTH and Cortisone research and to indicate in what direction this new understanding may lead us.

As Adolf Meyer so forcibly and adeptly pointed out, the mind is inseparable from the body in the process of growth, in the maintenance of health, and in the course of disease. Research work with ACTH and Cortisone, confirming this fundamental tenet of Dr. Meyer, has shown that these hormones are two of the many pathways for the maintenance of this intimate association.

The most obvious and characteristic

symptom of the psychiatric disorders is the disturbance in thinking. As far as we know, thinking, with its associated emotions, takes place on a cortical level. Thus, the symptoms of the psychiatric disorder represent a disturbance in cortical functioning. With the tools available to date, it has not been possible to measure or study this disturbance, other than by studying the symptoms presented to us by the patient. The actions of the pituitary and adrenal hormones have, however, indicated a mechanism by which these disturbances of the cortex are associated with biochemical and physiological disturbances[2,7]. The processes of enteroception and exteroception serve to give the cortex-adrenal system information necessary for the production of a steady state, in the sense of Walter Cannon's homeostasis. It is through this pathway that balance is maintained not only within the individual but also in the individual's adjustment to the environment. In the cortex, for instance, are represented the powerful drives of hunger, thirst and sex. Other drives related to and modified by the environment could also be shown, such as aggression, pleasure-seeking, reduction of anxiety, and self-preservation.

The findings in schizophrenia are particularly interesting. The investigations of Hoagland, Pincus, and associates[3,4,6] indicate that the schizophrenic patient has an unusually unresponsive adrenal cortex. This unresponsiveness of the adrenal cortex is seen, not only in their reaction to controlled stress situations but also in a lessened response to the injected corticotropic hormone. This is, however, not universally true of schizophrenics, but is more generally true in chronic cases where up to 50% of the patients may show unresponsive adrenal cortices. Furthermore, there is indication that although at rest there is no overall deficiency, there is a qualitative difference in the adrenocortical hormone output in the schizophrenic patient. This qualitative difference may be the crux of the matter.

It is impossible to tell the cart from the horse. We do not even know that a causal relationship exists. The unresponsive adrenal cortex of the chronic schizophrenic patient may be the result of his mental disturbance; the mental disturbance may be the result of the unresponsive adrenal cortex; or they may be associated findings without direct relationship. It would be a great stride ahead in our understanding of these psychoses if the nature of the association of mental disorders with changes in glandular physiology could be cleared up.

The suggestion that these findings might represent a state of exhaustion of the adaptation syndrome, as outlined by Hans Selye[8], does not at present seem to be the case. In the experimentally produced state of exhaustion ACTH will produce an adrenal response, while in the case of the schizophrenic, ACTH does not. Thus, it appears that the failure in the hormonal balance of the schizophrenic patient is at the level of the adrenal cortex, both quantitatively and qualitatively, and not at the level of the anterior pituitary.

Since their introduction, electric shock, metrazol shock, and insulin coma therapies have been used empirically without experimental or scientific rationale. Studies on ACTH and Cortisone have given us some new knowledge into the mechanisms of the therapeutic response seen with these rather drastic measures. It has been shown by Hoagland and associates[3] that electric shock therapy and insulin treatments act as powerful stimulants to the adrenal cortex, and furthermore that those patients with adrenal cortices

most responsive to adrenal corticotropic hormone show the greatest improvement when shock therapy is used. Thus, if this unresponsiveness of the adrenal cortices of those patients with a poor prognosis for therapeutic benefit by the shock therapies proves to be generally true, by giving ACTH and measuring the cortical hormone output we can select those patients most likely to do well on shock therapy. It is probable that these therapies stimulate the region of the hypothalamus along with the total motor stimulation, resulting in a temporary increase in ACTH output by the pituitary.

Up to this point we have been speaking of psychotic patients. All work to date fails to indicate any disturbance in the hypothalamic-pituitary-adrenal system in the psychoneurotic patient. The responses of their adrenal cortices in stress situations do not differ materially from the normal. There is no decrease in overall adrenal cortical hormone output, and their response to ACTH is unaltered.

The fact that these hormones fail to produce any therapeutic benefits in mental disorders does not mean that there are not certain mental attitudes associated with a diminished supply or an overabundance of these hormones in the body. Sprague[9] and associates at the Mayo Clinic pointed out that many of their arthritic patients being treated with ACTH or Cortisone showed a mood change characterized by an unusual sense of well-being. They felt that this was a false sense of well-being, and to the extent that it was false it was equivalent to the psychiatric symptom of euphoria. Now this was all very confusing, especially as in Cushing's syndrome, which is a disease produced by an overabundance of cortical hormone, euphoria is an infrequent symptom. Indeed rather the reverse is true: those suffering from Cushing's syndrome are usually mentally depressed, and only occasionally is garrulousness verging on euphoria present. However, one of their cases of arthritis treated with ACTH developed a moderately severe depression not unlike that seen in Cushing's syndrome, even though the arthritis improved greatly. On stopping the ACTH, this patient's arthritic symptoms rapidly returned, but the depression cleared up. There appears then, to be a two-sided effect upon the mental state of the individual. Why this reaction occurs is still unanswered. Our Department of Psychiatry is at present engaged[10] in a further study of the very interesting mental attitudes produced by the injection of these hormones.

To date 22 cases have received Cortisone here, and we have studied case records from additional medical centers. Most of the cases showed a general feeling of well-being and, in some instances, the patients noted that their outlook on life had changed markedly, usually toward the rosy side. Clear cut transient hypomanic states were sometimes (10 cases) found, but not always. Three patients became frankly psychotic on Cortisone, while 1 psychotic patient showed marked improvement. Deliroid reactions were also noted. It appears, then, that in some individuals Cortisone may precipitate a psychotic reaction; such a reaction should be watched for whenever Cortisone is being administered. Prompt but gradual restriction of dosage of the substances usually prevents the development of prolonged psychotic episodes.

In addition to the change in mental attitudes, one can more grossly detect cortical functioning changes in the EEG. Preliminary reports of Hoefer and Glaser[5] indicate that the electroencephalogram is altered by the administration of these hormones. At present, the Laboratory of Electroencephalo-

graphy of the Colorado Psychopathic Hospital is engaged in attempting a further elaboration on the nature and extent of the electroencephalographic changes associated with the use of Cortisone. In 8 cases studied, Busse[1] was unable to detect any EEG changes.

By way of summary, it would be well to point out where these investigations now stand and a few of the many problems that need further study. First, there is the associated lessened responsiveness of the adrenal cortices in some schizophrenic patients, particularly in the chronic cases. However, no causal relationship is known to exist, and it is possible that the mental symptoms of schizophrenia and the adrenal cortical changes are produced by a common disease process and that one is not the cause of the other. Hoagland[3] suggests that since potassium is so important for proper function of the nervous system and since the adrenal hormones are the prime regulators of potassium metabolism, some of the symptoms of the psychoses are related to disturbed potassium balance in the brain. And as Selye[8] points out, the mental symptoms of Addison's disease (fatigue, irritability, restlessness, insomnia, and failures in judgment) may be controlled by proper therapeutic attention to the potassium balance. This undoubtedly is not the whole answer, but it may be part of it. In any event, these findings may prove fruitful in leading us to a further understanding of the body changes associated with this severe mental disorder.

Second, even though in themselves ACTH and Cortisone do not produce any therapeutic response, convulsive therapies have been shown to have, as one of their effects, the stimulation of the pituitary and adrenal glands. Consequently, even though in some measure the responsiveness of the adrenal cortex to ACTH can be used to prognosticate the therapeutic response, it is unlikely that the beneficial effects of shock therapy are achieved entirely by this endocrine stimulation. Furthermore, the chronic case of schizophrenia, which is more apt to have an unresponsive adrenal cortex, would then fall into the group with a poor prognosis to shock therapy. To some extent this is borne out clinically, as it has been noted that in the acute or early phase of this illness, shock therapy is usually more successful. These correlations may prove to be an opening wedge toward increasing our understanding of the mechanisms of the therapeutic effects of electric shock and insulin coma therapy.

Third, it has also been shown that the psychoneurotic patient and the psychotic patient differ not only in their symptomatology, as seen by the psychiatrist, but also in their hormonal balances as measurable by the biochemist and the endocrinologist. To date, the psychoneurotic has failed to show any changes in the pituitary-adrenal system. Consequently, it is improper to include these psychoneurotic patients in the general adaptation syndrome as outlined by Hans Selye. While it is true that the psychoneurotic patient has difficulty in adapting to his environment and suffers from symptoms as the consequence, our tools and methods at present have been unable to detect an associated adaptation, or failure of adaptation, of the adrenal cortical mechanism.

Fourth, Cortisone and ACTH produce not only changes for the better in arthritis, gout, asthma, and so forth, but also changes in the mental attitudes. There are mood changes, swinging from depression to euphoria. The changes in the electroencephalograph may be related to the mood changes.

The Department of Psychiatry, University of Colorado Medical School, is actively engaged in a further study of the associated mental and nervous changes with Cortisone therapy. It is possible that this study may reveal a therapeutic tool for use in the major psychoses, which at present take such a dreadful toll of the population of this country.

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PROCEEDINGS OF

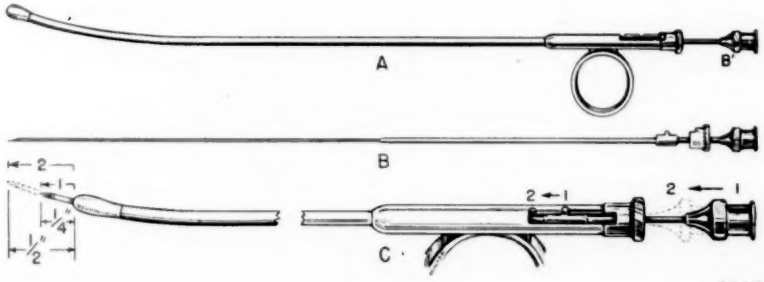
The Physiological Society of Philadelphia

SESSION OF NOVEMBER 21, 1950

The Enzymatic Conversion of Homogentisic Acid to 4-fumaryl Acetoacetate. ROBERT G. RAVDIN, M.D., and DANA I. CRANDALL, Ph.D. (Dept. of Biochem., School of Med., Univ. of Penna.) Homogentisic acid was shown to be quantitatively converted by a water soluble enzyme system prepared from mammalian liver homogenates into equimolar amounts of fumarate and acetoacetate. The enzyme system was separated by alcohol fractionation into 2 components: an oxidative, ring-opening enzyme that produced an 8-carbon aliphatic intermediate, and a hydrolysing enzyme that acted on the intermediate to produce the end products. The former enzyme is relatively stable and acts independently of the cytochrome system. The latter is probably identical with an enzyme, described by other authors, that hydrolyses 2,4 diketo acids and for which there has been no known natural substrate. The intermediate was isolated and characterized by elemental analysis, electrometric titration, and spectrophotometric studies, and appears to be 4-fumaryl acetoacetate.

The Clearance of Radioactive Sodium from the Body and Cervix of the Human Uterus as a Measure of Functional Uterine Blood Flow. MILTON L. MCCALL, M.D., and THEODORE SOPP, B.S. (Depts. of Obstetrics and Gynecology of the Jefferson Hosp. and Phila. Gen. Hosp., and Dept. of Radiology, Phila. Gen. Hosp.). In the search for a method for the study of uterine blood flow in the unanesthetized intact human subject, the clearance of radioactive sodium as used by Kety upon the gastrocnemius muscle was utilized.

An instrument was devised (Fig. 1) whereby the radioactive material could be injected directly into the myometrium of the fundus. The uterine needle cannula is the size of an ordinary uterine sound which is hollowed so as to allow the passage of a 22-gauge needle. The needle is drawn back during insertion through the cervix and endometrial cavity until the nose of the cannula fits snugly against the interior of the fundus. The needle is then pushed into the myometrium to any desired distance, usually ¼ inch, and injection carried out by means of an attached syringe.



In this study both the uterine fundus, using the uterine needle cannula, and the posterior lip of the cervix, using a 22-gauge needle to the depth of ½ inch, were used as sites of injections; 5 to 10 microcuries of Na^{24} in 0.5 cc. to 1.0 cc. of isotonic saline were injected. Calculations revealed that the amount of irradiation received at the point of injection as well as to the region of the ovaries and by the body as a whole was not significant. Immediately following injection a Geiger-Muller counter was placed over the mid-line of the lowermost portion of the abdomen and counts recorded every ½ minute until a final plateau was reached. The counts less the final background were plotted semilogarithmically against time, and straight lines resulted. The clearance constant (k) is a measure of the effective uterine blood flow.

Fourteen uteri were injected at various times during the menstrual cycle. The uterine blood flow appeared to be fairly constant during the majority of the cycle, increasing markedly toward the end of the cycle and abruptly decreasing after the first 2 days of menstruation. k varied from 0.10 to 0.385. Three retroverted uteri uniformly showed low constants of less than 0.1. Nine myomatous uteri of various sizes had constants varying from 0.04 to 0.65.

Entero-hepatic Circulation of Bromsulphalein. STANLEY H. LORBER, M.D., and HARRY SHAY, M.D. (Samuel S. Fels Res. Inst., Temple Univ. School of Med.). Significant variations in serum levels of bromsulphalein obtained in some patients following the 5 mg./kg. dose of the dye, when repeated at daily or weekly intervals, made the test difficult to interpret. This difficulty did not occur after the 2 mg./kg. dose. Since the duodenum may contain relatively high concentrations of bromsulphalein during the course of the test, an entero-hepatic circulation of the dye was considered as a possible explanation for these varations. This was investigated in afebrile, non-jaundiced, fasting subjects who remained supine during the tests. Three types of procedures were performed, using both the 2 and 5 mg./kg. doses.

Demonstrable blood levels of B.S.P. were obtained after duodenal instillation of the dye but were significant only after the 5 mg./kg. dose. Removal of bile containing dye by duodenal aspiration during the 5 mg./kg. intravenous test could reduce serum dye levels below those obtained when duodenal contents were not aspirated. This occurred only when a sufficient quantity of the administered dye was obtained in the aspirate. Cholecystectomized patients were administered the dye intravenously with and without common duct aspiration. There was little correlation between dye removal and change in serum B.S.P. levels when the 2 mg./kg. dose was employed, but after the 5 mg./kg. dose a close relationship was observed. This was evidenced by marked decreases in serum B.S.P. levels when a high percentage of the intravenously administered dye was recovered from the common duct. The effect of the reabsorbed dye upon serum levels was more readily evident after the intravenous administration of B.S.P. than after its intestinal instillation. This may be due to "saturation" of the excretory mechanism under the former conditions.

We conclude from these data that the influence of an entero-hepatic circulation upon the B.S.P. test is a quantitative one and suggests that the smaller dose is preferable for clinical use.

Skin Oxygen Tension and Arterial Oxygen Saturation in vivo; Similarity to the Oxygen Dissociation Curve of the Blood. RAYMOND PENNEYS, M.D. (Peripheral Vascular Sec., Robinette Found., Med. Clin., Hosp. Univ. of Penna.). Up to the present time, the relationship of arterial oxygen saturation to arterial oxygen tension has been studied by biochemical methods. These methods not only require much skill and time but also must be done *in vitro*. The development of the oxygen (polarographic) electrode, for measurement of the oxygen tension of the intact human skin (**Montgomery, H.**, and **Horwitz, O.**: J. Clin. Invest., **29**, 1120, 1950) and the oximeter, for measurement of the arterial blood oxygen saturation in the intact human ear, presented an opportunity to study this relationship, *in vivo* by simple methods.

Oxygen tension measurements were made in the vasodilated skin of the arm (skin temperature was between 31 and 34°C. and kept constant within 1°C., room temperature was 23.5 to 32°C.). In 21 experiments carried out on 9 normal subjects, the arterial oxygen saturation was increased, or decreased, by administering a gas of varying oxygen concentration (**Penneys, R., Thomas, C. B.**, and **McLean, R. L.**: Bull. Johns Hopkins Hosp., **84**, 430, 1949). At the following arterial saturations, the average oxygen tensions were as follows: at 90% arterial saturation, 64% of the room air reading; at 85% saturation, 51%; at 80%, 42%; at 75%, 39%; and at 70% saturation, 35%. At 98% arterial saturation the tension was 135%; at 99%, 180%; and at 100%, with continued inhalation of pure oxygen, 460% of the room air reading.

These data show that the oxygen tension of skin having a vasodilated skin bears the same type of relationship to the arterial oxygen saturation as does the arterial oxygen tension; this relationship can be expressed by the oxygen dissociation curve of blood obtained *in vitro*.

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BOOK REVIEWS AND NOTICES

THE FIRST ANESTHETIC. THE STORY OF CRAWFORD LONG. By FRANK KELLS BOLAND, M.D., Prof. of Clinical Surgery, Emory Univ. Pp. 160; 21 ills. Athens: Univ. of Georgia Press, 1950. Price, $3.00.

IT is generally recognized that Long performed the first surgical operation with ether on March 30, 1842, but not so well known that there were several witnesses present who later legally certified to the facts and that Long continued to use ether in subsequent operations, at least 5 having been performed before the celebrated Ether Day at the Massachusetts General Hospital in 1846. The Author, President of the Crawford W. Long Memorial Association, not only thoroughly documents these facts, but also points out that Long made no attempt to conceal the nature of the anesthetic, in sharp contrast to Morton's Letheon, the composition of which (sulphuric ether with the odor disguised by aromatic oils) he kept secret until forced to reveal it by George Hayward. Long, to be sure, erred in not publicizing his discovery, though not an easy task considering his surroundings; but we are inclined to agree with Dr. Boland that Long undoubtedly was the discoverer of ether as a surgical anesthetic in the ordinary sense of the word. Even under Dr. Welch's definition that "the accepted rule [is] that scientific discovery dates from public demonstration", a case can be made for Long's demonstration being a public one, made, as it was, before witnesses in a small town of a few hundred people. The history of medicine is punctuated with discoveries like this, and Mendel's for instance, that were not sufficiently demonstrated publicly to escape oblivion for many years. Boland's book gives many sidelights on the protagonists of the anesthesia discovery and suggests interesting conjectures as to how Jackson on his visits to Jefferson may have heard of the ether frolics and of Long's discovery and passed on the information to Morton. It is a curious coincidence, to say the least, that Jackson years later should have claimed to have made himself unconscious with ether just a month before the date of Long's operation on James Venable.

Boland's is undoubtedly a valuable contribution to the history of anesthesia, though not the last word in the celebrated ether controversy.

E. K.

ANXIETY IN PREGNANCY AND CHILDBIRTH. By HENRIETTE R. KLEIN, M.D., Assoc. in Psychiatry, Columbia Univ. Coll. of Physicians and Surgeons, HOWARD W. POTTER, M.D., Prof. of Psychiatry, Long Island Coll. of Med., and RUTH B. DYK, M.S. Pp. 111. New York: P. B. Hoeber, 1950. Price, $2.75.

THE Authors of this small book have reported on various emotional reactions that occur in connection with childbearing. They have considered, along with other things, specific attitudes, misconceptions, superstitions, anxieties. They have inquired into where these attitudes come from, whether they are inevitable, what role they play, how they affect pregnancy and delivery.

It is an important contribution and is a book worth noting, especially by psychiatrists and obstetricians.

W. P.

ARE PRISONS NECESSARY? By JOSEPH G. WILSON, M.D., Pp. 313. Phila.: Dorrance, 1950. Price, $3.00.

IF this book followed the theme suggested by its title and elaborated on the need for scientific methods of probation and parole to empty our jails and reclaim over half their population, it would indeed serve a useful purpose. In order to do this the probation officer should be in full touch with the parolee or probationer. This is impossible with the heavy case load that the average probation officer carries.

If probation were perfected, there would be a tremendous saving in money and increase in human salvage. The author devotes just 2 paragraphs to this subject.

Fifty pages of introduction are devoted to a discussion of crime and punishment largely historical and sanely presented. The rest of the book is devoted to the sex life of men and women in prisons. It is hard to see the purpose of all this. It panders to the prevailing curiosity about sex matters and may sell the book, but it does not add to our knowledge of psychiatry or sociology. Throughout there is evidence of a lack of social responsibility. What real doctor worthy of the guild would ever condone recommending suicide to a patient? (Page 193, or this with murder, page 245.) The Author states "What other advice could I give to this

patient?"—*i.e.*, to commit suicide. He could advise her to see another doctor who could solve her problem, and at the same time cure himself of the idea that because he cannot cure a patient, no one else can. This is a part of the prevailing paranoia of some modern psychiatrists. It is indeed not limited to psychiatrists.

This book cannot be recommended either to the general practising physician or the psychiatrist, on account of its lack of consistency and faulty scientific method. It cannot be recommended to the general public because the sex matter in the individual case reports would serve no useful purpose, and could do more harm than good.

D. McC.

MANUAL OF RHEUMATIC DISEASES. By W. PAUL HOLBROOK, M.D., and DONALD F. HILL, M.D. Pp. 182; 119 ills. Chicago: Year Book Publishers, 1950. Price, $4.25.

HERE, at last, is an excellent epitome of diagnosis and treatment in the field of rheumatology. Its conciseness without dogmatism has enabled the Authors to succeed where most others have failed. They present a clear summary of present day knowledge without becoming bogged down in long discussions of etiologic theories and other subjects of primarily academic interest. Practical points of diagnosis and treatment are emphasized. The format is excellent, the illustrations well chosen and clear, the arrangement is good, and the index is adequate.

This Reviewer is placing this readable book on the required list for his students.

J. H.

PLASTIC AND RECONSTRUCTIVE SURGERY: A MANUAL OF MANAGEMENT. By FERRIS SMITH, M.D., F.A.C.S., Consultant in Plastic Surgery, Blodgett Memorial Hospital, Grand Rapids, Michigan. Pp. 895; 592 ills. Phila.: W. B. Saunders, 1950. Price, $15.00.

THE American pioneers in plastic surgery are now bringing to fruition their experience gained in the past 30 to 40 years. The present volume is one of at least 10 recently published texts that fill a void in this specialty that has been felt not only by plastic surgeons but also by surgeons in other specialties who may be called upon to perform reconstructive work. Ferris Smith, who reports his experiences over the past 35 years, is especially noted for his application of the principle of "multiple excision" (Morestin) to eradicate skin defects, a procedure which he has developed to a high degree. Much of the work has already appeared in previous publications, but the present collection, with its well chosen bibliography, is invaluable as a reference book and a working guide.

The field of plastic surgery is so vast that there is hardly a publication that is all-inclusive. This text, as in the case of several others, is not complete, but it does offer the highly personalized opinions of the Author, and in this is its greatest value.

A high estimate is placed upon Doctor Smith's work; this book will be a much used addition to any surgeon's library.

H. R.

MR. CARLYLE: MY PATIENT. A PSYCHOSOMATIC BIOGRAPHY. By JAMES L. HALLIDAY. Pp. 227. New York: Grune & Stratton, 1950. Price, $3.50.

THIS combination of psychosomatic medicine and biography, written by a student and writer on psychosocial medicine, endeavors to construct from Thomas Carlyle's Reminiscences, augmented frequently by additions from the Author's imagination, a case history in the modern psychoanalytic style. Many a reader will early be repelled by the often fantastic and unnecessarily nasty phraseology and symbolic concepts of Freudian ideology, especially in Carlyle's so-called "oral and anal aggression" periods of infancy. One example will suffice: as one of Carlyle's earliest recollections, he speaks of "dim ruddy images of deeper and deeper brown shade." This the Author assumes to be the red of anger merging into "the color ranges of faeces." Scoptophilia, anal power, phallic potency and the like are linked with good-mother-child and paternal hostility impulses in improbable ways; even Carlyle's friendly relations with Edward Irving are twisted to appear as active homosexuality, quite unreasonably, as it seems to the Reviewer.

Most of the rest of the book shifts to an ordinary biography. Such are the discussions in the so-called Interludes, plain and, if uninspired, at least do not return to the earlier psychoanalytical jargon. Even the sections on Carlyle's views on society, politics and theology, and his "system of basic ideas" lead the reader to no new light or conclusions on his dyspeptic, insomniac and krotophobic existence. In short, the book will be no help to the medical man and irritating or repellent to the decent minded general reader for whom the book is said to have been primarily designed.

E. K.

THE PHYSICIAN'S BUSINESS: *Practical and Economic Aspects of Medicine.* By GEORGE D. WOLF, M.D., Assistant Clinical Professor of Otolaryngology, New York Medical College. Foreword by HAROLD RYPINS, A.B., M.D., F.A.C.P. 3d ed. Pp. 563; 96 ills. Phila.: J. B. Lippincott, 1949. Price: $10.00.

THIS book is full of useful and practical advice on a host of subjects about which medical students hear far too little, and which most doctors have to learn the hard way. The chapter headings tell the story: Internship and Residency; Specialization; Medical Careers other than Private Practice; Selecting a Location; Planning and Equiping an Office; Records; Fees: Instructions to Patients; Ethical Conduct; Medical Journalism; Forensic Medicine; Income Tax; Insurance; Social Medicine, and others. This 3d edition, with numerous references to the literature, is up to date and should be read with profit and interest by all medical students and young physicians.

R. K.

PRIMER OF ALLERGY: *A Guidebook for those who must find their Way through the Mazes of this Strange and Tantalizing State.* By WARREN T. VAUGHAN, M.S., M.D., with illustrations by JOHN P. TILLERY. 3d. ed., revised by J. HARVEY BLACK, M.D. Pp. 175; illustrated. St. Louis: C. V. Mosby, 1950. Price, $3.50.

THIS handy little volume, in addition to an adequate and clear presentation of the theory of allergy, contains a wealth of good advice for allergics, amusingly written and illustrated. This revised third edition should be welcomed by doctors and by their allergic patients as a very helpful manual.

R. K.

NOSES. By HAROLD M. HOLDEN, M.D., D.D.S., Ph.D. Pp. 252; 20 ills. Cleveland, Ohio: World Pub. Co., 1950. Price, $3.50.

TAKEN as a collection of material revealing chiefly the psychological importance of the Nose, this book provides much information on such varied aspects as the relation of the nose to character, to superstitions about life and death, sneezing, itching, the nose as a detective, its influence on the voice, and so on. The book is far, however, from being a "full length study of the human nose."

In long sections on physiognomy and the psychological angle, the Author wanders into much irrelevant matter, even though "as one of the country's foremost plastic surgeons" he has had good opportunity to observe the psychological damage that may follow facial deformity, whether congenital or acquired. One turns with relief to the anthology (74 pp.) of the nose in Art and Literature and in Caricature, including 3 pages of nasal idioms such as: "It's no skin off *my* nose"; "*il a bon nez*" (he is smart) and so on. The short chapter on The History of Plastic Surgery one would like to see longer.

One can easily visualize a busy, methodical surgeon filing notes on his hobby through many years. Then, having gratified his chief impulse, getting the material into publishable form with the least additional effort. While this may seriously detract from its excellence as a literary production, it has little bearing on its usefulness as a source of miscellaneous information in these days of psychosomatic emphasis, especially in view of its adequate index and rich bibliography.

E. K.

NEW EDITIONS

Nutrition and Diet Therapy. By FAIRFAX T. PROUDFIT, Univ. of Tennessee, and CORINNE HOGDEN ROBINSON, Temple Univ. 10th ed. Pp. 950. New York: Macmillan, 1950. Price, $4.00.

The Rheumatic Diseases. By G. D. KERSLEY, M.D., Bristol Royal Hosp. Foreword by SIR FRANCIS R. FRASER, M.D. 3d ed. Pp. 143; 53 ills. New York: Grune & Stratton, 1950. Price, $3.50.

THIS little compendium on rheumatic diseases contains some excellent discussions of the newer work. The discussions of treatment are mostly concise and well put, but the illustrations are not particularly well chosen or clear. The introduction is confusing, and does not contain a classification of the various rheumatic diseases. The book falls short of its expressed intent of epitomizing present knowledge of the rheumatic diseases.

J. H.

A Textbook of X-ray Diagnosis. By BRITISH AUTHORS. Edited by S. COCHRANE SHANKS, M.D., Univ. College Hosp., London. Vol. 4. 2d ed. Pp. 592; 553 ills. Phila.: W. B. Saunders, 1950. Price, $15.00.

THIS is the first of the 4 volumes of this 2d edition to appear. An inevitable increase in size to accommodate new material has necessitated the new arrangement into volumes dealing respectively with the head and neck, the chest, the abdomen, and bones and joints.

This standard text has long been recognized as one of the best and more definitive works on the subject. Volume 4 contains essentially the same material as in the chapters on bones and joints in the previous edition with pertinent additions in the form of text and plates. E. P.

Recent Advances in Chemotherapy. By G. M. FINDLAY, M.D. 3d ed. Vol. 1. Pp. 625. Phila.: Blakiston, 1950. Price, $7.50.

THIS edition will be published in 4 volumes. The 1st contains the chemotherapy of scabies, and of helminthic and protozoal diseases, except malaria. A valuable series testifying to the expanding scope of chemotherapy.

Nursing in Prevention and Control of Tuberculosis. By H. W. HETHERINGTON, M.D., Chief of Clinic, and FANNIE W. ESHLEMAN, R.N., B.S. Henry Phipps Institute, Univ. of Penna. 3d ed. Pp. 361; 12 ills. New York: G. P. Putnam's Sons, 1950.

DR. E. R. Long's Introduction stresses the timeliness of this new edition of a book that is uniquely valuable for the protection of nurses as well as for increasing their protection of patients.

Emergencies in Medical Practice. Edited by C. ALLAN BIRCH, M.D., Chase Farm Hosp., Enfield, England. 2d ed. Pp. 564; 131 ills., 8 in color. Balt.: Williams & Wilkins, 1950. Price, $5.50.

THIS book, written by several British specialists, will have but little appeal to physicians in this country because of the use of British proprietary trade names and references to the British Pharmacopoeia. The apothecary system is preferred. The editor correctly employs "ml." in preference to "cc." for fluid dosages in the metric system, yet he incorrectly employs the term "milligrams per cent" instead of "milligrams per 100 cc."

This diagnosis and management of acute pancreatitis, herniated nucleus pulposus, mumps, encephalitis, and diabetic coma are not in accord with modern concepts. There are no references to the employment of aureomycin or terramycin, but instructions for the use of dextran and tromexan are given. The advice to carry sulfathiazole solution and anti-diphtheritic serum in the physician's emergency bag would hardly meet with favor in this country.

Most of the emergencies are adequately described but methods of management advised will meet with greater favor in the British Isles than here.

J.L.

Surgery of the Eye: Injuries. By ALSTON CALLAHAN, M.D., Prof. of Ophthalmology, Med. Coll. of Alabama. Pp. 240; 367 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $11.50.

THIS book deals with the principles of the treatments of injuries of the eye in a thorough and authoritative manner. The Author has had wide experience with traumatic surgery of the eye as Chief of the Eye Section of the Northington General Hospital in Tuscaloosa. His book is well written, beautifully illustrated, and valuable for reference.

F.A.

Physicians Federal Income Tax Guide and Simplified Accounting Record. By HUGH J. CAMPBELL and JAMES B. LIBERMAN. Pp. 127. Great Neck, N.Y.: Donuger & Raughley, 1950, 1951. Price, $2.50.

NO physician preparing his own income tax return will fail to find in this excellent guide the information he seeks—and find it the more readily with an excellent Index and detailed Table of Contents. Few will fail to save themselves many times the price of the booklet.

NEW BOOKS

The Psychoanalysis of Elation. By BERTRAM D. LEWIN, M.D. Pp. 200. New York: W. W. Norton, 1950. Price, $3.00.

THIS book is by an important member of the American Psychoanalytic group and is a real contribution to psychoanalytic literature. It investigates the feeling of elation, excitement, mania, euphoria, and shows that elation is a defense and a resistance. Pathological happiness is interpreted as being a reliving of an early infantile state where reality and pleasure were interchangeable or undifferentiable experiences. There are 12 pages of references at the end. It is a scholarly work, of importance to psychiatrists and analysts.

W. P.

Annual Review of Biochemistry. Edited by J. MURRAY LUCK, HUBERT S. LORING, and GORDON MACKINNEY. Vol. 19. Pp. 596. Stanford, Cal.: Annual Reviews, 1950. Price, $6.00.

THIS 19th volume maintains the high standard of its predecessors in reporting recent advances (1949-1950). The reviews are on broad topics and contain full bibliographies that are valuable for the research worker. Their value to the casual reader is questionable, as every sentence is likely to contain several facts as well as references. Besides the standard reviews on enzymes, proteins, fats, carbohydrates and vitamins, new material on partition chromatography, the biochemistry of neoplastic tissue, the chemical composition of blood plasma and serum, and the biochemistry of antibiotics has been added.

M. B.

Genes, Plants and People. By C. D. DARLINGTON and K. MATHER, John Innes Horticultural Institution, London. Pp. 187; 13 figs. Phila.: Blakiston, 1950. Price, $4.00.

Favourite Prescriptions. Edited by SIR HENEAGE OGILVIE and WILLIAM A. R. THOMSON, M.D. Pp. 76. London: The Practitioner, 1950. Price, 4s.

Cybernetics. Edited By HEINZ VON FOERSTER. Trans. 6th Conference. Pp. 209. New York: Josiah Macy, Jr. Found., 1950. Price, $3.50.

Researches on the Measurement of Human Performance. By N. H. MACKWORTH. Med. Res. Council Spec. Rep. Ser., 268. Pp. 156; 58 figs. London: His Majesty's Stat. Off., 1950. Price, 4s.

Clinical Applications of Suggestion and Hypnosis. By WILLIAM T. HERON, Ph.D., Prof. of Psychology, Univ. of Minnesota. Pp. 116. Springfield, Ill.: Charles C Thomas, 1950. Price, $3.00.

Human Milk. Wartime Studies of Certain Vitamins and Other Constituents. By S. K. Kon and E. H. Mawson. Med. Res. Council Spec. Rep. Ser., 269. Pp. 188. London: His Majesty's Stat. Off., 1950. Price, 4s.

Heparin und Heparinoide Dicumarol. Von Dr. Th. Halse, Ass't der Chirugischen Univ. Frieburg/Br. Pp. 225; 38 ills. Zürich: S. Hirzel, 1950. Price, gan. fr. 13.50.

Laboratory Manual for Pharmacognosy. By Edward P. Claus, Ph.D., Prof. of Pharmacognosy, Univ. of Pittsburgh. 2d ed. Pp. 111. St. Louis: C. V. Mosby, 1950. Price, $3.25.

Basic Principles of Clinical Electrocardiography. By Hans H. Hecht, M.D., Assoc. Prof. of Medicine, Univ. of Utah. American Lect. Ser. 87. Pp. 88; 32 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $2.00.

The Causes of Blindness in England and Wales. By Arnold Sorsby. Med. Res. Council, No. 24. Pp. 42. London: His Majesty's Stat. Off., 1950. Price, 1s, 6d.

Problems of Infancy and Childhood. Edited by Milton J. E. Senn. Trans. 3d Conference. Pp. 156. New York: Josiah Macy, Jr. Found., 1950. Price, $1.25.

Twentieth Century Mental Hygiene. By Maurice J. Shore, *et al.* Pp. 444. New York: Social Sciences Publishers, 1950. Price, $6.00.

Le Diatesi Trombogene. By Orazio Giannico. Preface by Prof. Enrico Greppi. Pp. 163. Rome: Ditta Luigi Pozzi. Price not given.

Plant Biochemistry. By James Bonner, California Inst. of Technology. Pp. 537; illustrated. New York: Academic Press, 1950. Price, $6.80.

Antihistamines. Industry and Product Survey. By Nathan Wishnefsky, *et al.* Pp. 157. New York: Chemonomics, Inc., 1950. Price, $5.00.

Renal Function. Edited by Stanley E. Bradley. Trans. 1st Conference. Pp. 172; illustrated. New York: Josiah Macy, Jr. Found., 1950. Price, $2.50.

Selected Studies on Arteriosclerosis. By Rudolph Altschul, M.U. Dr., Prof. of Histology, Univ. of Saskatchewan. Pp. 182; 79 ills. Springfield, Ill.: Charles C Thomas, 1950. Price, $5.50.

This small volume is an interesting but rather disjointed collection of the Author's ideas, many not generally accepted, on the pathogenesis of human and cholesterol arteriosclerosis. The main theme is that the endothelial cell is the phagocytic cell involved in arterial cholesterol deposits and that it becomes transformed into the fibroblast during the proliferative phase.

The description and illustration of experimental atherosclerosis is excellent. Despite the fine format, the book is too expensive for its size. W.S.

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